The Preeclampsia Intervention with Esomeprazole (PIE) trial: A double blind, randomised, placebo-controlled trial to treat early onset severe preeclampsia

by

Catherine Anne Cluver

Dissertation presented for a PhD degree

Department of Obstetrics and Gynaecology,
Faculty of Medicine and Health Sciences
at Stellenbosch University

Supervisors: Professors Gerhard Theron, Susan Walker and Stephen Tong

April 2019

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes 3 original papers published in peer reviewed journals, published correspondence and 1 unpublished manuscript. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and for each of

the cases where this is not the case a declaration is included in the dissertation indication the

nature and extent of the contributions of co-authors.

Date: April 2019

Declaration by the candidate:

With regard to Chapter 2, the nature and scope of my contribution were as follows: I wrote the first draft of the protocol and was responsible for all edits to the protocol. I obtained ethical approval for the study and was the principle investigator for the study. I was responsible for patient identification, randomisation, data collection and data entering. I was responsible for shipping the biological samples. I wrote the first draft of the final manuscript and was responsible for all the edits and final version. I submitted the final manuscript for publication.

Nature of contribution Extent of contribution (%)

The following co-authors have contributed to Chapter 2:

Name	e-mail address	Nature of contribution	Extent of contribution (%)
Natalie J Hannan	[redacted]	Supervised the laboratory work	6%
Erika van Papendorp	[redacted]	Study research midwife	10%
Richard Hiscock	[redacted]	Trial Statistician	5%
Sally Beard	[redacted]	Laboratory analysis	2%
Ben Mol	[redacted]	Chair of Trial Steering Comittee	4%

Gerhard Theron	[redacted]	Supervisor of PhD project	4%
David R Hall	[redacted]	Co-investigator	2%
Eric Decloedt	[redacted]	Pharmacokinetic analysis	4%
Marietjie Stander	[redacted]	Supervised the pharmacokinetic laboratory work	2%
Kim T Adams	[redacted]	Laboratory work for the pharmacokinetic studies	1%
Megan Rensburg	[redacted]	Sample preparation and freezing	1%
Susan Walker	[redacted]	Supervisor of PhD	15%
Stephen Tong	[redacted]	Supervisor of PhD	15%

Signature of candidate:

Date: April 2019

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Chapter 2,

2. no other authors contributed to [specify chapter and page numbers in the dissertation] besides those specified above, and

3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in [specify chapter or part of a chapter and page numbers in the dissertation] of this dissertation.

Signature	**Institutional affiliations**	**Date**
[redacted] Natalie Hannan	University of Melbourne	19 December 2018
[redacted] Richard Hiscock	University of Melbourne	19 December 2018
[redacted] Sally Beard	University of Melbourne	19 December 2018
[redacted] Ben Mol	Monash University	19 December 2018

[redacted] Gerhard Theron	Stellenbosch University	19 December 2018
[redacted] David R Hall	Stellenbosch University	19 December 2018
[redacted] Eric Decloedt	Stellenbosch University	19 December 2018
[redacted] Marietjie Stander	Stellenbosch University	19 December 2018
[redacted] Kim T Adams	Stellenbosch University	19 December 2018
[redacted] Megan Rensburg	Stellenbosch University	19 December 2018
[redacted] Susan Walker	University of Melbourne	19 December 2018
[redacted] Stephen Tong	University of Melbourne	19 December 2018

DEDICATION

I dedicate this thesis to my family, namely my father Mr Albert Andrew Kendal Cluver, my husband Dr Andrew James Lawson and our children Natalie, Michaela and Daniel. Without their support this would not have been possible.

SUMMARY

This body of work addresses the clinical dilemma posed by preterm preeclampsia. Firstly, we tested a potential therapeutic (esomeprazole) for the treatment of early preterm preeclampsia in a double-blind randomised controlled trial. The primary outcome of interest was prolongation of gestation, with secondary outcomes including maternal and perinatal outcomes. Importantly, this study was underpinned by extensive pharmacokinetic and biomarker studies on both plasma samples and placental tissue. We found that a daily dose of 40mg of esomeprazole did not prolong pregnancy in early preterm preeclampsia and there were no differences in maternal or neonatal outcomes or markers of endothelial dysfunction. The esomeprazole concentrations that were observed in our participants were within the lower range of concentrations used in our preclinical *in vitro* studies. We therefore concluded that 40 mg may not have been sufficient to have efficacy in treating preterm preeclampsia, and future studies should consider the role of a higher dose or intravenous administration, which has a higher exposure over time and peak concentration.

Secondly, we assessed the impact of coexisting fetal growth restriction on pregnancy latency, obstetric, maternal and perinatal outcomes among women undergoing expectant management of early preterm preeclampsia. We found that the latency-to-delivery interval was significantly shorter among pregnancies with coexisting fetal growth restriction. These pregnancies were less likely to reach 34 weeks gestation and more likely to be delivered for suspected fetal compromise. More women with coexisting fetal growth restriction underwent an emergency caesarean section without a trial of labour induction and of those considered eligible for induction of labour, the rate of emergency caesarean section was higher among those with fetal growth restriction. Postnatally, the presence of coexisting fetal growth restriction was

associated with a higher rate of postnatal death and necrotising enterocolitis. Interestingly, the rate of maternal complications did not differ between the groups. We concluded that coexisting fetal growth restriction, diagnosed at the same time as preeclampsia, is an important determinant of pregnancy outcome among women being managed expectantly for early preterm preeclampsia.

Thirdly, we sought to determine the role of expectant management of preeclampsia and the hypertensive disorders of pregnancy after 34 weeks gestation by assimilating the available data in a Cochrane systematic meta-analysis. Based on the limited data available, maternal outcomes appear better with planned early delivery for hypertensive disorders after 34 weeks' gestation, but it is unclear whether this is associated with increased risks for the baby, especially at earlier gestations. It was not possible to determine whether planned early delivery was beneficial for different hypertensive conditions, particularly preeclampsia. We concluded that further studies are needed, preferably with reliable characterisation of hypertensive disease sub-types, to determine the ideal timing of delivery to optimise maternal and perinatal outcomes for hypertensive disorders of pregnancy occurring after 34 weeks gestation.

This research provides new information about a candidate therapeutic for the treatment of preeclampsia. Clinical aspects of the hypertensive disorders of pregnancy that could further improve management are also discussed.

OPSOMMING

Die inhoud van die werkstuk handel oor voortydse pre-eklampsie as ‘n kliniese probleem. Eerstens is ‘n potensiële terapeutiese middel (esomeprazol) vir die behandeling van voortydse pre-eklampsie getoets in ‘n dubble blinde ewekansige kliniese proef. Die primêre uitkoms van belang was verlenging van swangerskapsduurte, met moederlike en perinatale uitkomste as sekondêre uikomste. Daar was omvattende farmakokinetiese en biomerker studies op beide plasma en plasentale monsters gedoen gedoen. Ons vind dat ‘n daaglikse dosering van 40 mg esomeprazol nie swangskapsduurte met voortydse pre-eklampsie verleng het nie. Daar was ook geen verskille in moederlike en neonatale uitkomste en merkers van endoteel wanfunksie nie. Die esomeprazol konsentrasies soos waargeneem in deelnemers aan die studie was in die laer konsentrasie reikwydte van wat in die pre-kliniese in-vitro studies gebruik is. Ons gevolgtrekking is dus dat 40 mg nie voldoende was om pre-eklampsie te behandel nie. Toekomstige studies moet hoër of intraveneuse doserings oorweeg, met hoër blootstelling oor tyd en hoër piek konsentrasies.

Tweedens het ons die impak ondersoek van meegaande fetale groei inkorting op swangerskaps latensie, verloskundige, moederlike en perinatale uitkomste van vroue met voortydse pre-eklampsie wat afwagtend hanteer is. Ons het gevind dat die latensie-tot-verlossing tydsverloop betekenisvol korter was in swangerskappe met meegaande fetale groei inkorting. Die swangerskappe het minder dikwels 34 weke swangerskapsduurte bereik en verlossing was meer algemeen vir vermoedelike fetal nood. Meer vroue met fetale groei inkorting het nood keisernsitte ondergaan sonder ‘n proef van induksie van kraam. Die met fetale groei inkorting wat kwalifiseer vir induksie van kraam het ook ‘n hoër noodkeisersnit insidensie gehad. Nageboorte was fetale groei inkorting geassosieër met ‘n hoër nageboorte sterftekoers en

nekrotiserende enterokolitis. Moederlike komplikasies tussen die groepe het interessant genoeg nie verskil nie. Ons gevolgtrekking is dat meegaande fetale groei inkorting wat saam met die pre-eklampsie gediagnoeer word, ‘n belangrike bepaler van swangerskapsuitkoms is, indien vroue afwagtend hanteer word met voortydse pre-eklampsie.

Derdens het ons die waarde van afwagtende hantering van pre-eklampsie en hipertensiewe toestande van swangerskap na 34 weke swangerskapsduurte ondersoek deur beskikbare data te versamel in ‘n Cochrane oorsig. Die beperkte inligting dui daarop dat met hipertensiewe toestande na 34 weke swangerskapsduurte beplande vroeë verlossing moederlike uitkomste verbeter. Daar is onsekerheid of die hantering geassosieër is met verhoogde risikos vir die baba veral met vroeër swangerskapsduurte. Dit is ook nie moontlik om ‘n betroubare aanbeveling te maak oor beplande vroeë verlossing met verskillende hipertensiewe toestande, veral pre-eklampsie nie. Ons het tot die gevolgtrekking gekom dat verdere studies nodig is, met by voorkeur, betroubare beskrywing van die hipertensiewe siekte sub-tipe. Die ideale tydstip van verlossing kan dan bepaal word vir optimale moederlike en perinatale uitkomste van hipertensiewe toestande wat na 34 weke swangerskapsduurte ontwikkel. Die studies moet moederlike uitkomste soos mortaliteit, erge morbiditeit soos eklampsie, ‘n serebrovaskulêre ongeluk, pulmonale edeem, erge renale inkorting, lewer hematoom of ruptuur, lewerversaking, HELLP sindroom, diffuse intravaskulêre stolling, trombo-emboliese siekte en abruptio plasentae insluit. Perinatale uitkomste wat ingesluit behoort te word is fetale en neonatale sterftes, graad III of IV intravertrikulêre bloeding of intraserebrale bloeding, nekrotiserende enterokolitis, respiratoriese nood sindroom of graad III of IV hialiene membraan siekte, klein-vir-datum en neonatale konvulsies. Uitkomste wat ook ingesluit behoort te word is keisersnit insidensie en duurte van hospitaal verblyf van beide moeder en baba.

Die navorsing verskaf nuwe inligting oor ‘n kandidaat middel vir die behandeling van pre-eklampsie. Kliniese aspekte van hipertensiewe toestande van swangerkap wat hantering verder sal verbeter word ook bespreek.

Table of Contents

CHAPTER 1. Introduction

1.1 Background literature

1.1.1 Burden of disease

The hypertensive disorders of pregnancy are among the most common medical complications in pregnancy.[1] Preeclampsia, the most serious of these complications, remains a leading contributor to maternal and perinatal mortality and morbidity worldwide. Preeclampsia is estimated to be responsible for 70,000 maternal deaths and over 500,000 perinatal losses every year. Further, it is estimated that for every preeclampsia related death there are between 50-100 women who experience significant morbidity.[2] This burden is largely shouldered in low and middle income countries.[3] In South Africa, high maternal and child mortality rates are recognised as a leading contributor to the 'quadruple burden of disease', along with the Human Immunodeficiency Virus epidemic, high levels of violence and increasing rates of non-communicable disease. The hypertensive disorders of pregnancy remain a major contributor to maternal mortality in South Africa. They are responsible for 14% of maternal deaths and this proportion has not decreased over the past 20 years.[4]

1.1.2 Definitions and classification systems

There are many classification systems for the hypertensive disorders of pregnancy.[5–9] Most agree that hypertension in pregnancy is defined as systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg on the average of at least two measurements.

Severe hypertension is defined as systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg on at least two measurements.

The four main hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia on chronic hypertension.

Chronic hypertension is defined as hypertension that is present before 20 weeks gestation or predates the pregnancy. Chronic hypertension usually persists postpartum and can be classified as primary or secondary to an underlying medical disorder.

Gestational Hypertension is defined as hypertension that develops after 20 weeks of gestation without associated proteinuria or end organ involvement. It may progress during pregnancy to preeclampsia. The hypertension should resolve by 12 weeks postpartum and if not, the diagnosis of chronic hypertension is then made.

Preeclampsia is defined as the new onset of hypertension with significant proteinuria or end-organ dysfunction, with or without proteinuria, after 20 weeks of gestation in a previously normotensive woman. End organ dysfunction includes renal insuffiency (defined as a serum creatinine concentration of more than 1.1mg/dL or ≥97.2µmol/L or doubling of the creatinine concentration in the absence of other renal disease), thrombocytopaenia (defined as platelet count < 100 000/microliter), impaired liver function (defined as transaminases at twice the normal concentrations), pulmonary oedema or cerebral or visual symptoms.[9] The American College of Obstetricians (ACOG) does not include fetal growth restriction as evidence of end organ dysfunction but the International Society for the Study of Hypertension in Pregnancy (ISSHP) does. ISSHP also defines thrombocytopaenia as a platelet count less than 150 000/microliter.[6,9] Preeclampsia with severe features includes women with preeclampsia who have severe hypertension, new-onset cerebral or visual symptoms including photopsia, scotomata, severe

headache and an altered mental state, pulmonary oedema, severe epigastric or right upper quadrant pain and a platelet count of less than 100 000/microliter.[9]

Chronic hypertension with superimposed preeclampsia is defined by the new onset of significant proteinuria or end-organ dysfunction after 20 weeks gestation in a woman with underlying chronic hypertension. If a woman has chronic proteinuric hypertension before 20 weeks, superimposed preeclampsia is only diagnosed if there is significant loss of blood pressure control with an increase in proteinuria or end-organ dysfunction.

In some settings, particularly in middle- and low-income countries, a woman may only seek antenatal care after 20 weeks gestation. If they have hypertension or hypertension with proteinuria they are said to have unclassified hypertension or unclassified proteinuric hypertension.[10] The diagnosis is then reviewed 12 weeks postpartum and they are reclassified into one of the above groups.

In 2018 the International Society for the Study of Hypertensive Disorders in Pregnancy updated the guidelines and have discouraged the use of the terms severe preeclampsia or preeclampsia with severe features due to concerns that milder preeclampsia may be undertreated.[11]

Preeclampsia can also be classified according to the gestation that it arises. Preterm preeclampsia occurs before 37 weeks gestation and is further divided into early preterm preeclampsia (before 34 weeks gestation) and late preterm preeclampsia (between 34 weeks and 37 weeks gestation).[12] Term preeclampsia occurs after 37 weeks gestation. Other terminology commonly used to describe preeclampsia is early-onset versus late-onset disease, with early-onset disease defined as occurring before 34 weeks and late-onset disease after 34 weeks gestation.

1.1.3 Epidemiology

Hypertensive disorders of pregnancy complicate 5-10% of pregnancies worldwide. It is difficult to determine the true incidence, particularly in low to middle income countries, as most estimates are hospital based and do not include births that occur in the home or outside the hospital.[5] Of the hypertensive disorders of pregnancy, chronic hypertension comprises approximately 1%, gestational hypertension 3% and preeclampsia 2 to 4%.[3] Early preterm preeclampsia is less common and makes up less than a third of all cases of preeclampsia.[13] Most women with late-onset preeclampsia present after the 37th week of gestation.[14]

The incidence of hypertensive diseases in pregnancy appears to be increasing, most likely due to the increase in high population attributable risk factors, such as obesity and increasing maternal age.[15] Despite this, the incidence of eclampsia and other severe complications has decreased in high income countries, likely due to earlier detection and recourse to delivery.[16,17]

Most deaths associated with the hypertensive disorders of pregnancy are due to preeclampsia. Among preeclamptic deaths, risk factors for maternal mortality include increasing maternal age, the need for preterm delivery and nulliparity. Black women and women who received no antenatal care are at higher risk of severe morbidity and mortality.[18] The vast majority of preeclampsia related deaths occur in low income countries where there is limited access to health care facilities.[19–21] Deaths in preeclampsia are most commonly due to cerebrovascular events (38.7%) and in particular intracerebral haemorrhage.[22]

Other complications resulting in mortality include cardiac failure resulting in pulmonary oedema, renal failure, liver rupture or haemorrhage and haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome.

For every maternal death, it is estimated that 20 to 30 women suffer severe morbidity and 50 to 100 suffer significant morbidity.[2,23] As with mortality, the morbidity associated with preeclampsia is largely shouldered in low- and middle-income countries.[23] Maternal morbidities associated with the hypertensive diseases of pregnancy include neurological complications like eclampsia, stroke, retinal detachment and blindness, acute renal failure, pulmonary oedema, a hepatic haematoma with a possible rupture, HELLP syndrome and placental abruption. Adverse perinatal outcomes associated with the hypertensive disorders of pregnancy include stillbirth, neonatal death and fetal growth restriction.[24] Perinatal outcomes associated with preeclampsia are significantly influenced by gestational age at delivery, particularly in low and middle income countries where access to advanced neonatal care is limited. While chronic hypertension and preeclampsia have been associated with an increased risk of preterm birth, it is preeclampsia that is the most significant contributor.[25,26]

1.1.4 Pathogenesis

The pathogenesis of preeclampsia is not completely understood, is multifactorial and involves maternal, fetal and placental contributors. Placental tissue is nevertheless a prerequisite for developing the disease as evidenced by its association with gestational trophoblastic disease and cases of postpartum preeclampsia with retained products.[27–29]

Placental hypoperfusion resulting in hypoxia and ischaemia are key factors in the development of all preeclampsia. In early preterm preeclampsia defective trophoblast infiltration results in abnormal remodelling of spiral arteries with defective placentation and hypoperfusion. In late-onset preeclampsia an increasing placental mass without an increasing placental blood supply can result in hypoxia and ischaemia.[30–34] The unifying downstream event is the elevated release of antiangiogenic factors, including soluble fms-like tyrosine kinase 1 (sFlt-1) and possibly soluble endoglin (sEng), from the ischaemic hypoperfused placenta. These circulating anti-angiogenic molecules are thought to cause widespread endothelial injury, [35–40] resulting in hypertension and end organ damage.

1.1.5 Management of preeclampsia

Early preterm preeclampsia

There is currently no medical treatment available for preeclampsia aside from delivery. Preeclampsia is a progressive disorder and delivery is always in the best interests of the mother. At preterm gestation, this poses a particular dilemma, as clinicians are often forced to deliver early to prevent disease progression and major morbidity in the mother, but in doing so, expose the infant to the serious complications of prematurity. In particular, fetuses delivered severely preterm (at less than 32 weeks' gestation) are at significant risk of death, or survival with severe disability including neurodevelopmental delay.[41] It is for these reasons that expectant management of preeclampsia is undertaken at preterm gestation in carefully selected cases.

The aim of expectant management is to prolong gestation to benefit the fetus without risking maternal compromise. It is reasonable to offer expectant management from 24 weeks gestation depending on the accepted threshold for viability at the institution.[42–44] In our setting, expectant management of early preterm preeclampsia is offered from 26 weeks.[45] Two large observational studies have also supported the role of expectant management of early preterm preeclampsia, both reporting maternal safety.[46,47] Expectant management is usually undertaken in a tertiary unit with a dedicated team and access to a theater for emergency deliveries. Before expectant management is undertaken the mother is stabalized over a period of 24 to 48 hours and if major complications like eclampsia, pulmonary oedema, HELLP syndrome, clinical or moderate to severe ascites on ultrasound, renal impairment and fetal compromise are found, the pregnancy is delivered. Expectant management involves inpatient management with 4-hourly blood pressure checks, a clinical examination twice a day, fetal monitoring, and routine blood work twice a week. All women are delivered at 34 weeks, or earlier if there is maternal or fetal compromise.[45]

Three randomised trials have evaluated the role of expectant management versus expedited delivery. The first trial, by Odendaal et al. at Tygerberg Hospital, South Africa included 58 women with a gestational age between 28 and 34 weeks. There was a seven day gain in gestation with a decrease in the number of infants needing ventilation in the group managed expectantly.[42] The second trial, by Sibai et al in North America, included 94 women with a gestational age between 28 and 32 weeks. In that trial, gestation increased by 15 days in the expectantly managed group, with a resultant decrease in neonatal intensive care admissions, respiratory distress syndrome and neonatal complications. Reassuringly, both these trials showed no increase in maternal complications. The third trial, the MEXPRE Study, from 8 sites in Latin America included 267 women who had severe preeclampsia with end organ symptoms like headache, visual disturbances, epigastric pain or more than 5 grams pf proteinuria. There was a significant

prolongation of pregnancy of 10 days versus 2 days in the expectantly managed group but no significant neonatal benefit. There was no difference in maternal morbidity although more placental abruptions were reported in the group managed expectantly. [48]

Expectant management aims to safely prolong gestation for the fetus and improve neonatal outcome, while not placing the mother at risk for severe complications.[45] Currently there are no predictors for which pregnancies are more likely to have a longer latency while being managed expectantly.[49] Two studies have assessed antenatally diagnosed fetal growth restriction as a possible predictor for adverse outcomes and have shown a shorter prolongation of pregnancy in women with preeclampsia and coexisting fetal growth restriction in women being managed expectantly for preterm preeclampsia.[50,51] These studies have been limited by their retrospective design, and have not determined whether the presence of coexisting fetal growth restriction is associated with worse perinatal and maternal outcomes.

Late preterm preeclampsia

For pregnancies complicated by preeclampsia and other hypertensive disorders of pregnancy in the late preterm period (34 weeks- 37 weeks), the perinatal benefits of prolonging gestation are more modest, and the risk-benefit equation is weighted toward maternal safety.[52,53] This creates uncertainty about the optimal gestation for delivery versus expectant management. Traditionally the management of preeclampsia after 34 weeks gestation has been a planned delivery, but there is currently a tendency to offer expectant management in the absence of maternal or fetal complications. Planned early delivery may prevent maternal complications and prevent poor fetal outcomes like stillbirth, yet expectant

management may decrease the risks of prematurity for the neonate. These complications include respiratory distress syndrome, the need for ventilation and neonatal intensive care admission.

The uncertainty on timing of delivery is best addressed by synthesising all available trial data that have examined perinatal and maternal outcomes in late preterm preeclampsia. This informs clinical management, as well as the design of any future interventional trials of potential therapeutic interventions for late preterm preeclampsia.

1.1.6 Therapeutic interventions for preeclampsia

The benefits of expectant management in preeclampsia would be maximized if there was a therapeutic agent available that could slow or arrest disease progression, allowing the fetus to safely gain gestation while minimizing maternal risk. Efforts to find a potential therapeutic for preeclampsia continue. Preeclampsia is characterized by maternal systemic inflammation and coagulation activation. Recombinant human activated protein C has been assessed in an open-label, single arm safety and efficacy trial.[54] Reducing the quantity of the angiogenic factors sFlt-1 and sEng is currently the most promising approach for preeclampsia. Reducing circulating sFlt-1 and sEng has been addressed in two main ways; systemic removal by plasma apheresis or using agents that reduce placental production and release of sFlt-1 and sEng.

Two small pilot studies have assessed serial apheresis treatments to target the removal of sFlt-1 from women with preterm preeclampsia. The first trial showed a reduction in sFlt-1 accompanied by stabilization of blood pressure and a reduction in proteinuria.[55] The second trial showed a stabilization in

sFlt-1 levels at baseline level.[56] Both trials showed prolongation in pregnancy and no adverse maternal outcomes. A third trial, the Proof-of-Concept Trial on Selective Removal of sFlt-1 in Pregnant Women with Preeclampsia Via Apheresis (SAVE), is currently recruiting 23 women at 5 sites in the United Kingdom (NCT02923206).

Recent preclinical laboratory studies have shown that proton pump inhibitors (PPI), particularly esomeprazole, have diverse biological actions making them a possible therapeutic for preeclampsia.[57] Esomeprazole decreases sFlt-1 and soluble endoglin production and release from primary trophoblast cells, as well as placental tissue explants and primary endothelial cells/tissues in both normal and preeclamptic pregnancies. Esomeprazole was also able to dilate whole human vessels from both normal pregnancies treated with a vasoconstrictor and vessels obtained from women with preeclampsia. These preclinical studies showed that esomeprazole had the additional advantage of decreasing endothelial dysfunction. Interestingly, in an in vitro model of tumor necrosis α–induced endothelial injury, the addition of esomeprazole reduced expression of endothelial vascular cell adhesion molecule-1, and reduced leucocyte adhesion to the endothelium. In vivo animal studies have also suggested that esomeprazole reduces blood pressure in a transgenic mouse model of preeclampsia where human sFlt-1 is overexpressed in the placenta and released in excess into the maternal blood, mimicking human preeclampsia.[58] Shafik et al have also shown that esomeprazole improved systolic blood pressure and prolonged the gestational period of preeclamptic rats.[59] Subsequent to these laboratory findings, Saleh et al has reported that circulating sFlt-1 levels were lower among pregnant women at risk of developing preeclampsia who were coincidentally taking PPIs, compared with women who were not taking PPIs.[60] This key human data supports the laboratory findings that PPIs may be a candidate treatment for

preeclampsia, and is independent validation of the concept. Together, these findings suggest the potential for esomeprazole as a novel therapeutic agent for preterm preeclampsia.

1.2 Purpose and scope of the research

This body of work addresses the clinical dilemma posed by preterm preeclampsia in three ways. Firstly, our research team tested a potential therapeutic for the treatment of early preterm preeclampsia (esomeprazole) in a double-blind randomised controlled trial. The primary outcome of interest was prolongation of gestation, with secondary outcomes including maternal and perinatal outcomes. Importantly, this study was underpinned by extensive pharmacokinetic and biomarker studies on both plasma samples and placental tissue. Secondly, members of our research team assessed the impact of coexisting fetal growth restriction on pregnancy latency, obstetric, maternal and perinatal outcomes among women undergoing expectant management of early preterm preeclampsia. Thirdly, the role of expectant management of preeclampsia and the hypertensive disorders of pregnancy after 34 weeks gestation was determined by assimilating available data in a Cochrane review

1.3 Overall Objective

This thesis addresses the management of preeclampsia remote from term, where we have tested a novel therapeutic for the treatment of preterm preeclampsia, identified fetal predictors of pregnancy outcome in preterm preeclampsia undergoing expectant management and evaluated the benefits of expectant management versus delivery in late preterm preeclampsia.

1.4 Hypotheses

The following hypotheses were addressed in this thesis:

1. That esomeprazole is an effective therapeutic for early preterm preeclampsia, allowing safe prolongation of gestation, without increasing maternal or fetal adverse outcomes; (Chapter 2)
2. That the presence of coexisting fetal growth restriction is an important predictor of pregnancy latency and outcome among women undergoing expectant management for early preterm preeclampsia; (Chapter 3)
3. That there is no significant difference between perinatal or maternal outcomes with expectant management of late preterm preeclampsia (Chapter 4)

Each of the chapters begins with an overview of the work and is followed by published and unpublished manuscripts. The work consists of 3 peer reviewed published articles, published correspondence and one unpublished manuscript.

CHAPTER 2. Esomeprazole to treat women with preterm preeclampsia

2.1 Overview

There is no known treatment for preeclampsia apart from delivery. This is particularly devastating for pregnancies complicated by early preterm preeclampsia where clinicians are often forced to deliver a premature infant to reduce the risk of maternal morbidity and mortality. If a treatment were available that temporizes disease progression, it could be used to safely delay delivery and gain gestation, thereby decreasing the degree of prematurity and improving perinatal outcomes without putting the mother's life at risk. Such a treatment would have the greatest impact in low income countries like South Africa, where the disease burden is high, and recourse to preterm delivery is limited by access to advanced neonatal care.

In pregnancies complicated by preeclampsia the placenta releases antiangiogenic factors which include soluble fms-like tyrosine kinase 1(sFlt-1) and soluble endoglin (sEng) into the maternal circulation which result in widespread endothelial damage. This results in the end organ disease seen in preeclampsia.

Esomeprazole, a proton pump inhibitor, which is widely used in pregnancy to treat gastric reflux, has shown promise as a potential candidate therapeutic in preclinical studies. Esomeprazole has been shown to potently decrease sFlt-1 and sEng production and release from trophoblast and endothelial cells, dilate whole blood vessels, decrease endothelial dysfunction and decrease blood pressure in a transgenic mouse model of preeclampsia.[57]

These promising preclinical data encouraged us to perform a double-blind randomised controlled trial to assess a daily dose of 40 mg of esomeprazole for the treatment of early preterm preeclampsia. We published the trial protocol (section 2.2) and prospectively registered the trial with the Pan African Clinical Trials Registry. The trial was approved by the South African Medicines Control Council and Stellenbosch University Health Research Ethics Committee.

We recruited 120 women at Tygerberg Hospital with pregnancies complicated with early preterm preeclampsia at a gestational age between 26 weeks and 32 weeks between January 2016 and April 2017. This is possibly the fastest recruitment rate for a treatment trial of preterm preeclampsia. The primary outcome was a prolongation of gestation by 5 days in the esomeprazole group. Secondary outcomes were maternal, neonatal and biochemical outcomes. We were the first to incorporate circulating markers of endothelial dysfunction associated with preeclampsia and pharmacokinetic studies in a preeclampsia treatment trial.

There were no between-group differences in median time from randomization to delivery: median 11.4 days (interquartile range, 3.6-19.7 days) in the esomeprazole group and 8.3 days (interquartile range, 3.8-19.6 days) in the placebo group (3 days longer in the esomeprazole arm; 95% confidence interval, -2.9 to 8.8; P=.31). There were no differences in maternal or neonatal outcomes or markers of endothelial dysfunction apart from a non-significant trend toward reduced placental abruption in the esomeprazole group. Esomeprazole and its metabolites were detected in maternal blood among those treated with esomeprazole at concentrations around the lower ranges tested in the in vitro laboratory studies. Reassuringly, only trace amounts were found in the umbilical cord blood.

We concluded that daily esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase 1 concentrations. The esomeprazole concentrations that were observed in our participants were in the lower range of concentrations used in our preclinical in vitro studies. Thus, 40 mg of esomeprazole may not be sufficient to have efficacy in treating preterm preeclampsia, and future studies should consider the role of a higher dose or intravenous administration, which has a higher exposure over time and peak concentration.

This chapter consists of the published trial protocol (Cluver et al 2015 BMJ Open)[61] and the published trial manuscript (Cluver et al 2018, AJOG).[62] Subsequent published correspondence, as well as the full trial protocol (including the patient information leaflet and consent form) can be found in the appendices.

2.2 Published protocol

BMJ Open

Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol

Catherine A Cluver,[1,2] Susan P Walker,[3] Ben W Mol,[4] Gerard B Theron,[1] David R Hall,[1] Richard Hiscock,[5] N Hannan,[2,3] S Tong[2,3]

To cite: Cluver CA, Walker SP, Mol BW, *et al*. Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol. *BMJ Open* 2015;5:e008211. doi:10.1136/bmjopen-2015-008211

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-008211).

Received 16 March 2015
Revised 1 September 2015
Accepted 6 October 2015

For numbered affiliations see end of article.

Correspondence to
Dr Catherine A Cluver;
cathycluver@hotmail.com

ABSTRACT

Introduction: Pre-eclampsia is a major complication of pregnancy, globally responsible for 60 000 maternal deaths per year, and far greater numbers of fetal losses. There is no definitive treatment other than delivery. A drug that can quench the disease process could be useful to treat early onset pre-eclampsia, as it could allow pregnancies to safely continue to a gestation where fetal outcomes are significantly improved. We have generated preclinical data to show esomeprazole, a proton pump inhibitor used for gastric reflux, has potent biological effects that makes it a worthwhile therapeutic candidate. Esomeprazole potently decreases soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin secretion from placenta and endothelial cells, and has biological actions to mitigate endothelial dysfunction and oxidative stress.

Methods and analysis: We propose undertaking a phase II, double blind, randomised controlled clinical trial to examine whether administering 40 mg esomeprazole daily may prolong gestation in women with early onset pre-eclampsia. We will recruit 120 women (gestational age of 26+0 to 31+6 weeks) who will be randomised to receive either esomeprazole or an identical placebo. The primary outcome will be the number of days from randomisation to delivery. Secondary outcomes include maternal, fetal and neonatal composite and individual outcomes. Maternal outcomes include maternal death, eclampsia, pulmonary oedema, severe renal impairment, cerebral vascular events and liver haematoma or rupture. Neonatal outcomes include neonatal death within 6 weeks after the due date, intraventricular haemorrhage, necrotising enterocolitis and bronchopulmonary dysplasia. We will examine whether esomeprazole can decrease serum sFlt-1 and soluble endoglin levels and we will record the safety of esomeprazole in these pregnancies.

Ethics and dissemination: This study has ethical approval (Protocol V.2.4, M14/09/038, Federal Wide assurance Number 00001372, IRB0005239), and is registered with NHREC (ID 3649) and the Pan African Clinical Trial Registry (PACTR201504000771349). Data will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitation of this study

- This is a protocol for a randomised, double blind, placebo controlled clinical trial.
- This is the first trial to assess whether esomeprazole is a treatment option for pre-eclampsia.
- We plan to recruit 120 participants and we have designed this study to be sufficiently powered to identify a prolongation of pregnancy.
- It may be underpowered to show improvements in maternal and perinatal outcomes. Therefore, if the trial yields a positive result, a larger subsequent multicentre study may be needed.

INTRODUCTION

Pre-eclampsia is one of the most serious complications of pregnancy, affecting 3–8% of pregnancies worldwide and is a leading cause of maternal and fetal/neonatal morbidity.[1–3] Pre-eclampsia is estimated to cause more than 60 000 maternal deaths annually.[4] There is no treatment that can quench the disease progression and the only treatment option available to arrest the disease is delivery of the pregnancy.[5] For pre-eclampsia occurring at preterm gestations, clinicians are often forced to deliver early on maternal indications to prevent major maternal morbidity, but in doing so, inflict severe prematurity on the fetus. In particular, fetuses delivered at less than 33 weeks' gestation are at significant risk of severe disability including cerebral palsy, stroke (intracerebral bleeding), retinopathy of prematurity, chronic lung disease and death.[6 7]

If an affordable and safe treatment was available that could temporise the disease progression of pre-eclampsia, clinicians could safely delay delivery and gain gestation to improve fetal outcome. This could save the lives of many infants and decrease the hospital burden caused by iatrogenic

prematurity. Such a treatment would be in keeping with the United Nations Millennium Development Goals to reduce child mortality and improve maternal health.[8]

The pre-eclamptic placenta releases antiangiogenic soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) into the maternal circulation. These factors are responsible for causing widespread maternal endothelial dysfunction and organ injury seen in clinical disease.[9] In addition, pre-eclampsia is strongly associated with placental and systemic oxidative stress.

Esomeprazole is a proton pump inhibitor widely used to treat women with gastric reflux in pregnancy. Large observational studies including administration during the first, second and third trimesters have not identified associations with adverse pregnancy outcomes, notably teratogenesis.[10–12]

We have performed preclinical laboratory studies where we have identified esomeprazole as a promising candidate therapeutic for pre-eclampsia. Esomeprazole potently decreased sFlt-1 and sEng secretion from placenta and endothelial cells, has strong actions mitigating endothelial dysfunction and has antioxidant properties. (A manuscript reporting this preclinical data has been submitted elsewhere and this work was recently presented.)[13]

OBJECTIVES

The primary objective is to examine whether a single daily dose of 40 mg of esomeprazole can safely prolong gestation in women with early onset pre-eclampsia diagnosed 26+0–31+6 weeks who are being managed expectantly, compared with expectant management alone.

The secondary objectives are to determine whether esomeprazole can improve maternal, fetal and neonatal outcomes, and to determine whether esomeprazole can significantly decrease levels of circulating sFlt-1 and/or sEng. Furthermore, we will examine whether esomeprazole is safe and well tolerated in the mother and infant.

Box 1 Inclusion criteria

A diagnosis of one of the following:
- Pre-eclampsia[14]
- Gestational hypertension with evidence of pre-eclampsia
- Pre-existing hypertension with evidence of pre-eclampsia
- Unclassified proteinuric hypertension

AND

All of the following is present:
- Gestational age between 26+0 and 31+6 weeks
- Estimated fetal weight by ultrasound between 500 and 1800 g (if gestation is not certain)
- Singleton pregnancy
- The managing clinicians have made the assessment to proceed with expectant management and that delivery is not expected within 48 h
- The managing clinician and neonatologist believe that the fetus could potentially be delivered in a viable condition
- No suspicions of a major fetal anomaly or malformation
- Patient will be admitted to hospital for expectant management and standardised care

METHODS

The full protocol is included as supplementary information (see online supplementary information 1).

Study design

Phase II hospital-based, double blind, randomised, placebo-controlled trial.

Study population

Pregnant women diagnosed with early onset pre-eclampsia at a gestational age between 26+0 and 31+6 weeks at Tygerberg hospital (Western Cape Provence of South Africa) will be invited to participate. To be enrolled, the treating team needs to have determined after their initial assessment that delivery is unlikely to be required within 48 h. A starting point of 26+0 weeks has been chosen as this would be the earliest gestation that Tygerberg Hospital would consider to be viable and are suitable to be offered expectant management.

Inclusion criteria

We will recruit women with a singleton pregnancy diagnosed with pre-eclampsia, defined according to the criteria published by the International Society for the Study of Hypertension in Pregnancy (ISSHP).[14]

We will seek to recruit those with pregnancies at a gestational age between 26+0 and 31+6 weeks, determined by either period dates (if the women is certain of her last menstrual period) or by an early, or mid trimester pregnancy ultrasound. If the gestational age is uncertain, we will recruit participants with an estimated fetal weight between 500 and 1800 g, determined by ultrasound performed at presentation. At Tygerberg Hospital we would not consider a pregnancy to be viable under 500 g and we would not offer expectant management if the fetal weight was above 1800 g.

To be eligible for this study, the treating clinicians need to have made an initial assessment and deemed that the patient is suitable for expectant management, that the fetus would benefit from expectant management and that immediate delivery is not required. A full list of the inclusion criteria is shown in box 1.

Exclusion criteria

Exclusion criteria include women with established maternal or fetal compromise that necessitates delivery, the current use of a proton pump inhibitor, contraindications to the use of a proton pump inhibitor or the use of medications that may interact with proton pump inhibitors. A full list of the exclusion criteria is shown in box 2.

Randomisation and allocation concealment

Randomisation will be done in an equal ratio of esomeprazole to placebo. An online, web-based sequence

Box 2 Exclusion criteria

Any of the following at the initial assessment:
- Patient is unable or unwilling to give consent
- Established fetal compromise that necessitates delivery
- The presence of: Eclampsia
- Severe hypertension
- Cerebrovascular event
- Posterior reversible encephalopathy syndrome
- Severe renal impairment
- Pulmonary oedema
- Left-sided heart failure
- Disseminated intravascular coagulation
- Platelet count $<50\times10^9$
- Haemolysis, elevated liver enzymes and low platelets syndrome
- Liver transaminases >500 IU/L
- Liver haematoma or rupture
- Severe ascites

Current use of a proton pump inhibitor
- Contraindications or a hypersensitivity reaction to the use of a proton pump inhibitor
- Current use of a drug that may be affected by a proton pump inhibitor

generator system will be used. It will be linked with codes for placebo and treatment tablets provided by the manufacturer contracted to produce the trial medication. Both the researchers and participants will be blinded.

The gestational age at diagnosis is likely to affect allowable length of pregnancy prolongation. To ensure treatment group allocation is balanced for this potential variable, we will stratify randomisation into two strata based on gestational age. Strata 1 includes a gestational age of 26+0 up to and including 28+6 weeks (500–1200 g if gestation is unknown). Strata 2 includes a gestational age of 29+0 up to and including 31+6 weeks (1200–1800 g if gestation is unknown). Thus, randomisation will include blocking within each gestational age stratum. We propose using blocks of 4–6 with the size and order randomly assigned.

Once the participants have been randomised, the treatment pack with the same code will be allocated to the participant. All treatment packs will be identical and will contain either active tablets or placebo. The researchers will have no access to the randomisation list. This process will ensure that there is allocation concealment throughout the conduct of the trial.

Participant enrolment

Participants will be identified after they have been admitted to Tygerberg Hospital (tertiary referral centre) with a diagnosis of early onset pre-eclampsia for expectant management. An information leaflet will be given to all potential participants and informed consent will be obtained (see online supplementary information 2 and 3). Each participant will be given an individual treatment pack containing either esomeprazole or placebo which will be produced by a contracted manufacturer IDT pharmaceuticals (http://en.idtaus.com.au). Labelling, storage and preparation will be done according to the requirements of the Medicines for Human Use (Clinical Trials) regulations.

Intervention

Participants will be randomised to daily administration of either active tablets containing 40 mg of esomeprazole or an identical placebo tablet orally once a day. Participants will remain under the care of the hospital treating team, and the study will not alter or interfere with the care given routinely to women with early onset pre-eclampsia, including on when to deliver.

Routine expectant management for pre-eclampsia

Expectant management for early onset pre-eclampsia involves admission to hospital, and close maternal and fetal surveillance. Maternal surveillance includes four hourly blood pressure measurement, twice daily clinical assessment, daily urinalysis and twice weekly assessments with blood tests (full blood count, renal function tests and hepatocellular enzymes if haemolysis, elevated liver enzymes and low platelets syndrome is suspected) and 24 h urinary protein measurement on admission. Fetal surveillance includes ultrasound assessments to assess growth of the fetus, the amniotic fluid index and fetal well-being including Doppler velocimetry of the umbilical artery, the ductus venosus and the middle cerebral artery. If there are no signs of fetal growth restriction or fetal compromise, the ultrasound is repeated two weekly to ensure there has been adequate trajectory of fetal growth. If there are signs of fetal growth restriction or fetal compromise, the frequency of ultrasound surveillance will be increased. Six hourly cardiotocographs are performed to assess the ongoing fetal condition. We will follow the Tygerberg Hospital protocols to monitor preterm fetal growth restriction and delivery may occur on fetal grounds if required.

All participants will receive two doses of β-methasone 24 h apart to reduce the risks of neonatal respiratory distress syndrome, intracranial haemorrhage and necrotising enterocolitis. A single repeat dose is usually given 1 week later. Most participants will be on antihypertensive treatment with the aim to stabilise the systolic blood pressure between 140 and 150 mm Hg and the diastolic blood pressure between 90 and 100 mm Hg. The medications used to treat the blood pressure will be documented. All women should already be receiving calcium, iron and folic acid supplementation.

Clinical care will be left up to the discretion of the clinical team. The indication for delivery will be a clinical decision. Indications for delivery may include failure to control blood pressure, the development of major maternal or fetal complications, or intrauterine fetal death. Expectant management will usually end at a gestation of 34 weeks.

Sample size and stratification according to gestation at recruitment

The reported duration that fetuses remain in utero after diagnosis of preterm pre-eclampsia is a mean of 11 days (SD of 7 days) and a median 9 days (range of 1–47 days).[15] These data are derived from a descriptive study on expectant management of early onset pre-eclampsia at Tygerberg Hospital, where we propose to undertake this study.[15] For 90% power, with a two-sided α set of 0.05, 43 patients are required in each group to identify a gain in gestation of 5 days. Given these data were skewed, the sample size has been multiplied by 1.15 to statistically correct for non-normality.[16] This increases the number required to 50 per arm. An additional 10 per arm will be added to allow for drop-outs. Thus, a total of 120 participants will be recruited to provide sufficient power to examine our primary outcome. (Power calculation performed using PASS V.12 software. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA).

Sample collection

Blood samples will be routinely collected twice a week. Two sets of specimens will be drawn, the routine pre-eclamptic monitoring samples and the trial samples. The routine blood samples include measurements of the haemoglobin, the platelet count and the urea and creatinine levels. These will be used by the managing clinicians to determine disease severity and may trigger delivery. The second set of samples will be the trial blood samples. These samples will be stored and will only be measured after delivery of the patient. These include measurements of sFlt, sEng and endothelin 1. These results will not be made available to the managing clinicians and will not affect management.

There are few data available on the pharmacokinetics of esomeprazole in pregnancy. In healthy males, the plasma elimination half-life is approximately 1–1.5 h and the peak plasma concentration occurs within 1–4 h after dosing. We propose to perform pharmacokinetic testing on a subgroup to determine if there are differences in the pregnant population. Fifteen patients in each group will undergo pharmacokinetic testing, so that blinding and allocation concealment is not affected. Blood will be drawn from an indwelling catheter in a forearm vein at 5 min before the medication is given (reference sample) and then at the following dosing interval: 15, 30 and 45 min and then at 1, 1, 5, 2, 4, 8 and 24 h after the initial dose is given. The sampling will be repeated on day 5.

Urine samples will be collected two times per week and sent for spot protein: creatinine ratios. 24 h protein excretion is routinely measured only once on admission but for the purposes of this study we will repeat it weekly. Cord blood and placental samples will be collected at delivery.

Withdrawal from the study

All participants will be informed that they are free to withdraw from the study at any time, and that this will not affect their clinical care. Basic clinical data and samples already collected will be included in the analyses in accord with the consent obtained at trial entry.

Duration of the trial

It is anticipated that the study can be completed in approximately 4 years (2015–2018). This study has been registered with NHREC (South African Human Research Ethics Committee) and PACTR (Pan African Clinical Trials Registry).

Ethical approval and dissemination

Data will be presented at international conferences and published in peer-reviewed journals.

Confidentiality

Patient confidentiality will be protected according to the regulations set forth by Stellenbosch University's Human Research Ethics Committee or Institutional Review Board (IRB).

OUTCOMES

The primary outcome is to examine whether 40 mg of daily esomeprazole can prolong a pregnancy complicated by early onset pre-eclampsia. We have powered the study for a further 5-day prolongation. This surrogate primary outcome marker has been chosen as it provides a sample size that is feasible and attainable for a phase II trial to test efficacy. Powering the trial to neonatal outcomes would require far greater numbers. If esomeprazole is proven to be effective, this trial would then form the basis for a larger multicentre trial powered to detect meaningful improvements in neonatal outcomes.

The secondary outcomes include maternal, fetal and neonatal mortality and morbidity, maternal serum biomarkers (including sFlt, sEng and endothelin 1) and placental samples (see boxes 3–5 for more information regarding secondary outcomes). We will present a composite outcome of the important maternal outcomes which include maternal death, eclampsia, pulmonary oedema, severe renal impairment or the need for dialysis, cerebral vascular event and the development of a liver haematoma or rupture. Other maternal outcomes will be compared as individual outcomes as listed in box 3. We will present a composite outcome for fetal outcomes. This will include poor prognostic signs on ultrasound, significant changes on the cardiotocograph that necessitate delivery, intrauterine fetal demise and growth restriction (see box 4). The composite outcome for neonatal outcomes will include neonatal death within 6 weeks after the due date, severe intraventricular haemorrhage, necrotising enterocolitis or bronchopulmonary dysplasia. Individual neonatal outcomes will be compared as listed in box 4. We will measure weekly the biomarkers sFlt, sEng and endothelin 1 which are antiangiogenic factors likely to play a role in the maternal endothelial dysfunction that is central to the

Box 3 Maternal secondary outcomes

Maternal outcomes
Composite outcome:
- Maternal death
- Eclampsia
- Pulmonary oedema
- Severe renal impairment or dialysis
- Cerebral vascular event
- Liver haematoma or rupture

Individual outcomes:
- Admission to a high care or intensive care unit
- Posterior reversible encephalopathy syndrome
- Left ventricular failure
- Serum creatinine >125 µmol/L
- Proteinuria >3 g/24 h
- Severe hypertension
- Disseminated intravascular coagulation
- Platelet count less than 50×109
- Haemolysis, elevated liver enzymes and low platelets syndrome
- Liver transaminases >500 IU/L
- Placental abruption
- Mode of delivery
- Use of antihypertensive agents
- Major postpartum haemorrhage
- Thromboembolic disease
- Moderate or severe ascites

pathophysiology of pre-eclampsia (ie, it would be advantageous if treatments can decrease circulating levels of these circulating factors). Esomeprazole levels will be tested on a selected subgroup to determine if the pharmacokinetics are altered in pregnancy. Esomeprazole levels will also be determined in the cord blood to assess placental transfer. The placenta will be examined histologically, and we will quantify mRNA and protein expression of haeme oxygenase-1 (HO-1) and sFlt-1 and sEng will be measured (see box 5). HO-1 is an endogenous antioxidant protein that may be beneficial in pre-eclampsia. We postulate placental HO-1 will be upregulated by esomeprazole. mRNA will be quantified by quantitative PCR, and protein will be quantified by western blot and densitometric analysis of the band obtained on the gel blot.

Box 4 Fetal and neonatal secondary outcomes

Fetal and neonatal outcomes
Fetal composite outcome:
- Reversed α-wave in the ductus venosus
- Significant changes in heart rate patterns
- Intrauterine fetal demise
- Fetal growth restriction
- Persistent reversed flow in the umbilical artery
- Redistribution in the middle cerebral artery

Neonatal composite outcome:
- Neonatal death within 6 weeks after the due date
- Grade III or IV intraventricular haemorrhage
- Necrotising enterocolitis
- Bronchopulmonary dysplasia

Neonatal individual outcomes:
- APGAR score <7 at 5 min
- Umbilical artery pH <7.05
- Umbilical artery lactate
- Surfactant use
- Neonatal intensive care or special care unit admission
- Intubation and mechanical ventilation
- Continuous positive airway pressure support
- Grade III/IV hyaline membrane disease
- Length of oxygen treatment
- Hospital stay
- Incidence of retinopathy of prematurity
- Neonatal sepsis

Box 5 Secondary biomarker outcomes

Maternal plasma:
- Maternal plasma
- Soluble fms-like tyrosine kinase 1 (sFlt-1)
- Soluble endoglin
- Placental growth factor (PGF)
- Endothelin 1
- (These analytes will be measured in serial samples collected during expectant managements)

Placental samples:
- Haeme oxygenase-1
- sFlt-1
- Vascular endothelial growth factor
- PGF
- Hypoxia inducible factor-1 α
- (mRNA and protein levels will be measured in these placental samples taken at delivery)

Data management and statistical analysis

Data will be collected prospectively. Data entry and checking will be continuous and queries will be followed vigorously to ensure clarification without delay.

The analyses will be on an intention-to-treat principle with comparisons made between proton pump inhibitors and placebo, for primary and secondary outcomes. Comparisons will be expressed as relative risks or mean differences with 95% CIs.

The patient characteristics, by treatment group, will be presented as mean (SD), median (25th—75th centile), minimum, maximum and count (%) depending on type and distribution. Significance level is set at 0.05 and all hypothesis testing will be two-sided.

The primary outcome will not be adjusted for multiple comparisons, but the secondary outcomes will be adjusted for multiple comparisons using a small number of prespecified outcomes. Two analyses are planned: (1) primary intention-to-treat analysis and (2) a treatment received analysis to examine response among those who actually took the tablets. The primary outcome (prolongation in days) between treatment groups will be tested using analysis of covariance regression analysis with both treatment group and gestational strata as

covariates. If a fetus does demise during expectant management, we will give it a length of pregnancy prolongation of zero and will include it in the primary outcome analysis.

Results will be presented as mean group difference with 95% CIs. Standard regression diagnostics and transformation of primary outcome, to achieve adequate distributions of residuals, will be performed if indicated. Survival analyses (ie, time until delivery), using Cox proportional hazards regression and Kaplan-Meier survivorship curves will be used.

The secondary outcomes may be composite or single outcomes. Continuous variables will be compared using either t test (for normally distributed variables) or Mann-Whitney U (non-normally distributed). Categorical values will be compared using χ^2 test. For the longitudinal data of plasma sFlt-1, sEng and endothelin 1 levels, we will (1) graph the data longitudinally, (2) compare levels between the groups relative to gestational age (3), compare levels between groups relative to days after recruitment and (4) compare levels between groups at delivery. Finally, the placental expression of sFlt-1, sEng and HO-1 will be compared using simple statistics.

Adverse events

Reporting and handling of adverse events and serious adverse events will be in accordance with the good clinical practice guidelines.[17]

Unblinding

Given the safety profile of esomeprazole in pregnancy has been well documented, we anticipate the need for unblinding will be very uncommon. However, we will have the following procedures in place should unblinding be required. Sheets with lists of 50 randomisation codes each will be sealed in individual, signed, numbered envelopes. If unblinding is requested, the relevant envelope will be opened by a person not involved in the trial in the presence of two witnesses, the group allocation read and the list resealed in an envelope and signed. The randomisation envelopes will be accessible at all times to the principal investigator who will be contactable by mobile telephone. The principal investigator will coordinate this process.

Early termination of the trial

If for any reason there is a need to stop the trial prematurely, this decision will be taken by the Data and Safety Monitoring Committee.

DISCUSSION

Pre-eclampsia is a serious life-threatening condition for both the mother and fetus and is associated with severe maternal and perinatal morbidity. If a treatment were to be discovered, it would have a major impact on both maternal and perinatal health. An ideal drug would ameliorate the biological disease process of pre-eclampsia in the mother and placenta, reduce the risk of serious complications from developing and allow pregnancies that were complicated by the disease at an early gestation to gain gestation without putting the mother and fetus at significantly increased risk.

However, there is currently no treatment besides delivery of fetus and placenta. Furthermore, there have been very few candidate-proposed treatments that have reached human trials. Thadhani *et al*[18] proposed the use of apheresis (or dialysis) to reduce the sFlt-1 fraction in the blood as a means to treat pre-eclampsia. That was a case series of eight patients where three had serial apheresis treatments with a possible prolongation of the pregnancy as a result. However, this is perhaps too invasive a treatment to be widely used to treat pre-eclampsia and its usefulness still remains unproven. As a result of preclinical studies, mainly on animal models, the anticholesterol drug pravastatin is being evaluated as a possible treatment for pre-eclampsia (STAMP trial, UK-based study).[19] We are not aware of other significant trials of orally available small molecules to treat pre-eclampsia.

It is known that the pre-eclamptic placenta releases antiangiogenic sFlt-1 and sEng into the maternal circulation, causing widespread maternal endothelial dysfunction and organ injury.[9] Pre-eclampsia is also associated with oxidative stress. A drug that can decrease sFlt-1 and sEng production, decrease endothelial dysfunction and oxidative stress may be a potential treatment for pre-eclampsia. We have generated preclinical data suggesting esomeprazole may have such actions. On the basis of this preclinical data, we are now proposing to undertake this phase II randomised clinical trial.

We propose recruiting 120 women at Tygerberg Hospital, in the Western Cape Provence of South Africa. There are two advantages to running the trial at this site. South Africa has a very high incidence of pre-eclampsia. Second, Tygerberg Hospital is a tertiary referral centre with a neonatal intensive care unit, a maternal critical care unit, an adult intensive care unit and an academic centre that actively contributes to the global scientific literature. Thus, we believe running this trial at Tygerberg Hospital represents a balance between obtaining sufficient number of cases of preterm pre-eclampsia, and offering modern obstetric and perinatal care, making the results potentially generalisable to both developed and developing countries.

Pravastatin is undergoing a randomised clinical trial in women with early onset pre-eclampsia (STAMP trial) and for women at risk of developing pre-eclampsia.[19 20] However, pravastatin has been assigned to pregnancy category X by the Food and Drug Administration (FDA) categorisation system and database for prescribing medicines in pregnancy. The FDA classifies category X drugs in pregnancy as medications where studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on

adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.[21] Esomeprazole is classified as a category C drug in pregnancy by the FDA. Category C is for drugs where animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in human, but potential benefits may warrant use of the drug in pregnant women despite potential risks.[21] Esomeprazole may very well then be a safer option than pravastatin for treating pre-eclampsia.

Additional safety information on the use of proton pump inhibitors in pregnancy is also now available as they have been extensively used in pregnancy for the treatment of gastro-oesophageal conditions. Large population-based cohorts and systematic reviews (including administration in the first trimester) have not found any adverse effects in pregnancy and specifically, these studies have not shown any increased risk for congenital abnormalities, spontaneous miscarriage or preterm delivery. The most recent systematic literature review which was published in 2009 included 1530 pregnancies exposed to proton pump inhibitors and had 133 410 non-exposed matched controls.[10] The largest study to date, published in 2010, spanned a 13-year period and involved 840 968 pregnancies of which 5082 were exposed to proton pump inhibitors in the first trimester of pregnancy. This study concluded that exposure to proton pump inhibitors, even during the first trimester of pregnancy, was not associated with an increased risk of major birth defects.[12] In 2012, a further large study involving 112 022 pregnancies of which 1186 pregnancies that had been exposed to proton pump inhibitors confirmed there was no associated increase risk for congenital anomalies with proton pump inhibitor use. Importantly this study also found no increase in fetal growth restriction or adverse neonatal outcomes (including premature delivery and low Apgar scores) in pregnancies exposed to proton pump inhibitors in the first, second or third trimesters of pregnancies.[11] Thus, esomeprazole is likely to be safe in pregnancy. Furthermore, we will also only be using treatment for a relatively short period in the late second and early third trimesters, well past the time of organogenesis.

We have powered our study to the primary outcome, which is to show esomeprazole can safely prolong gestation for five days. We believe such a gain of gestation in preterm pre-eclampsia is likely to result in significantly better neonatal outcomes. However, a limitation in this trial is that we have not specifically powered to detect improvements in maternal, fetal or neonatal outcomes (although these are planned secondary outcomes). The trial would need to be significantly larger to detect such clinical improvements. Given esomeprazole has not been used to treat pre-eclampsia before, it seemed more pragmatic to first undertake the trial as planned. If this trial yields a positive result, a further phase III multicentre randomised trial may be required to be sufficiently powered to demonstrate improvements in clinical outcomes.

A further potential novelty of this trial is that we will measure biomarkers that reflect disease severity. We will measure circulating levels of sFlt-1 and sEng in serial samples obtained from the mother. These antiangiogenic factors are considered to play an important role in inciting maternal endothelial dysfunction and end-organ injury seen in pre-eclampsia. Their importance as biomarkers is highlighted by the fact that in the STAMP trial, the primary outcome is to examine whether pravastatin can decrease circulating sFlt-1 levels in the mother. Furthermore, we will measure expression of key molecules in the placental samples obtained at delivery.

Pre-eclampsia kills mothers, fetuses and neonates and is responsible for severe maternal and neonatal morbidity. This is especially the case in the developing world where there is a lack of resources, including staff, equipment and finances. Currently there is no treatment apart from delivery. If a treatment were to be discovered it would have dramatic effects on maternal and neonatal outcomes. Esomeprazole has shown potential as a therapeutic agent in preclinical work on pre-eclampsia. Further advantages of esomeprazole are that it is available in tablet form, is safe during pregnancy and is not expensive. This makes it an ideal candidate as a global therapeutic for pre-eclampsia. It is therefore imperative for this trial to be performed. If esomeprazole were proven to be effective at prolonging gestation in early onset pre-eclampsia it would be the first treatment option for this group of vulnerable mothers and could play an important role in decreasing the clinical burden of this dangerous condition.

Author affiliations
[1]Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
[2]Translational Obstetrics Group, University of Melbourne, Mercy Hospital for Women, Melbourne, Victoria, Australia
[3]Department of Obstetrics and Gynaecology, Mercy Hospital for Women, University of Melbourne, Heidelberg, Victoria, Australia
[4]The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia, Australia
[5]Department of Anaesthetics, Mercy Hospital for Women, University of Melbourne, Melbourne, Victoria, Australia

Acknowledgements The authors would like to acknowledge Professor Jane Norman and Justus Hofmeyr for their contributions to the protocol development.

Contributors CAC, SPW and ST developed and designed the trial. SPW and ST obtained funding for this trial. CAC, SPW and ST wrote the first draft of this manuscript. RH helped with the statistical aspects of this protocol. NH was involved in the design of the laboratory arm of this trial. All authors were involved in revision of the manuscript. All authors approved the final version to be submitted. CAC and ST responded to the reviewers comments.

Funding This work is supported by the Kilvington Trust, The Medical Foundation for Mothers and Babies and The Shiela Handbury Foundation. NHMRC provides salary support to ST and BWM.

Competing interests None declared.

Ethics approval This study has ethical approval (protocol number M14/09/038 Federal Wide assurance number 00001372, Institutional Review Board number IRB0005239) registered with NHREC (Application ID 3649) and the PACTR and has the South African Medical Control Council approval (MCC trial reference 20150309).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The full protocol, patient information leaflet and consent forms are available as supplementary files. For further information please contact CAC by email: cathycluver@hotmail.com

REFERENCES

1. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. *JAMA* 2002;287:3183–6.
2. ACOG Committee on Obstetric Practice. Practice bulletin# 33: diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002;99:159–67.
3. Dolea C, AbouZahr C. *Global burden of hypertensive disorders of pregnancy in the year 2000. Evidence and information for policy (EIP)*. Geneva: World Health Organization, 2003.
4. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science* 2005;308:1592–4.
5. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;365:785–99.
6. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol* 2003;102:181–92.
7. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy* 2003;22:203–12.
8. United Nations Millenium Development Goals. http://www.un.org/millenniumgoals/ (accessed Feb 2015).
9. Levine RJ, Maynard SE, Qian C, *et al*. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672–83.
10. Gill SK, O'Brien L, Einarson TR, *et al*. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol* 2009;104:1541–5.
11. Matok I, Levy A, Wiznitzer A, *et al*. The safety of fetal exposure to proton-pump inhibitors during pregnancy. *Dig Dis Sci* 2012;57:699–705.
12. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med* 2010;363:2114–23.
13. Onda K, Hannan N, Beard S, *et al*. Proton Pump inhibitors for treatment of preeclampsia Abstract 6-OR. *XIX Word Congress ISSHP*; 26–29 Oct 2014.
14. Magee LA, Pels A, Helewa M, *et al*. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens* 2014;4:105–45.
15. Hall DR, Odendaal HJ, Steyn DW, *et al*. Expectant management of early onset, severe pre-eclampsia: maternal outcome. *BJOG* 2000;107:1252–7.
16. Ryan TP. Sample Size Determination and Power. Hoboken, New Jersey: John Wiley and Sons, Inc; 2013.
17. World Health Organization. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. *WHO Tech Rep Ser* 1995;850:97–137.
18. Thadhani R, Kisner T, Hagmann H, *et al*. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. *Circulation* 2011;124:940–50.
19. Ramma W, Ahmed A. Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia. *J Reprod Immunol* 2014;101-102:153–60.
20. Costantine MM, Tamayo E, Lu F, *et al*. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced preeclampsia. *Obstet Gynecol* 2010;116:114–20.
21. Teratology Society Public Affairs Committee. FDA classification of drugs for teratogenic risk. *Teratology* 1994;49:446–7.

2.3 Published manuscript

OBSTETRICS

Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial

Catherine A. Cluver, MMed; Natalie J. Hannan, PhD; Erika van Papendorp, BN; Richard Hiscock, MBBS; Sally Beard, BSc; Ben W. Mol, PhD; Gerhard B. Theron, MD; David R. Hall, MD; Eric H. Decloedt, MMed; Marietjie Stander, PhD; Kim T. Adams, BSc; Megan Rensburg, MMed; Pawel Schubert, MPhil; Susan P. Walker, MD; Stephen Tong, PhD

BACKGROUND: Preterm preeclampsia has a high rate of fetal death or disability. There is no treatment to slow the disease, except delivery. Preclinical studies have identified proton pump inhibitors as a possible treatment.
OBJECTIVE: The purpose of this study was to examine whether esomeprazole could prolong pregnancy in women who have received a diagnosis of preterm preeclampsia.
STUDY DESIGN: We performed a double-blind, randomized controlled trial at Tygerberg Hospital in South Africa. Women with preterm preeclampsia (gestational age 26 weeks+0 days to 31 weeks+6 days) were assigned randomly to 40-mg daily esomeprazole or placebo. The primary outcome was a prolongation of gestation of 5 days. Secondary outcomes were maternal and neonatal outcomes. We compared circulating markers of endothelial dysfunction that was associated with preeclampsia and performed pharmacokinetic studies.
RESULTS: Between January 2016 and April 2017, we recruited 120 participants. One participant was excluded because of incorrect randomization, which left 59 participants in the esomeprazole and 60 participants in the placebo group. Median gestational age at enrolment was 29+4 weeks gestation. There were no between-group differences in median time from randomization to delivery: 11.4 days (interquartile range, 3.6–19.7 days) in the esomeprazole group and 8.3 days (interquartile range, 3.8–19.6 days) in the placebo group (3 days longer in the esomeprazole arm; 95% confidence interval, −2.9–8.8; $P=.31$). There were no placental abruptions in the esomeprazole group and 6 (10%) in the placebo group ($P=.01$, $P=.14$ adjusted). There were no differences in other maternal or neonatal outcomes or markers of endothelial dysfunction. Esomeprazole and its metabolites were detected in maternal blood among those treated with esomeprazole, but only trace amounts in the umbilical cord blood.
CONCLUSION: Daily esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase 1 concentrations. Higher levels in the maternal circulation may be needed for clinical effect.

Key words: esomeprazole, trial, preterm preeclampsia, sFlt1, pharmacokinetics

Preeclampsia is one of the most serious complications of pregnancy. It affects 3–8 % of pregnancies and is a leading cause of maternal, fetal, and neonatal morbidity.[1,2] There is no treatment that can slow disease progression, and the only treatment option is to deliver the pregnancy. For preeclampsia that occurs at preterm gestations, clinicians are often required to deliver the fetus early, which results in iatrogenic prematurity with a risk of major disability that includes cerebral palsy, intracerebral bleeding, retinopathy of prematurity, chronic lung disease, and death. The risks of these complications are higher if pregnancies are delivered at earlier gestations.[3] If a treatment were available that temporizes disease progression, it could be used to safely delay delivery to gain gestation, thereby decreasing the degree of prematurity and improving perinatal outcomes.

The preeclamptic placenta releases elevated levels of soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin into the maternal circulation.[4] These antiangiogenic factors cause maternal endothelial dysfunction, hypertension, and multiorgan injury.[5] Esomeprazole is a proton pump inhibitor (PPI) that is prescribed widely in pregnancy to relieve symptomatic gastric reflux. Members of our team have performed preclinical laboratory studies that have shown that PPIs such as esomeprazole are a candidate therapeutic for preeclampsia.[6] Esomeprazole, in particular, has been shown to have diverse biologic actions. Firstly esomeprazole decreases sFlt1 and soluble endoglin production and release from primary trophoblast cells and placental tissue explants and primary endothelial cells/tissues in both normal and preeclamptic pregnancies. Secondly esomeprazole was able to dilate whole human vessels from both normal pregnancies treated with a constrictor and vessels that were obtained from women with preeclampsia. Thirdly, preclinical studies also showed that esomeprazole decreased endothelial dysfunction by mitigating tumor necrosis α–induced endothelial injury, as demonstrated by reducing expression of endothelial vascular cell adhesion molecule-1 and reduced leucocyte adhesion to the endothelium. Lastly important animal studies clearly show that esomeprazole reduces blood pressure in a transgenic mouse model of preeclampsia in which human sFlt1 is overexpressed in the placenta and released in excess into the maternal blood, as seen in women with preeclampsia.[6] Others have subsequently found decreased circulating sFlt1 and soluble endoglin levels in an existing cohort of bloods of women with suspected or confirmed preeclampsia that were coincidentally taking PPIs.[7]

Cite this article as: Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial. Am J Obstet Gynecol 2018;219:388.e1-17.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.07.019

AJOG at a Glance

Why was this study conducted?

Preeclampsia has high rates of fetal death or disability. There is no treatment to slow the disease, except delivery. Preclinical studies have identified proton pump inhibitors as a possible treatment.

Key findings

Daily oral esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase 1 concentrations.

What does this add to what is known?

This is the first trial for preterm preeclampsia that has integrated clinical outcomes, mechanistic studies, and pharmacokinetics. Oral esomeprazole (40 mg) may be too low a dose to treat preterm preeclampsia; higher doses may still be effective. This may be the fastest completed randomized clinical trial of a treatment for preterm preeclampsia. It is possible to complete clinical trials for preterm preeclampsia in a reasonable timeframe by running the trials in settings in which the incidence of disease is high.

These promising preclinical data suggest that esomeprazole is a potential candidate treatment; we therefore set out to examine whether oral esomeprazole may be an effective treatment for preterm preeclampsia.

Methods

Trial design

In this single-site phase II double-blind, randomized, placebo-controlled clinical trial, we compared oral esomeprazole with placebo. A 40 mg daily dose was selected based on pharmacokinetic data that showed effective suppression of gastrointestinal symptoms in nonpregnant patients and on reassuring data that showed no adverse effects if taken during pregnancy.[8-11] The trial site was Tygerberg Hospital, Cape Town, South Africa, which is a large academic referral center that is situated in a region with high rates of preeclampsia. We have published the protocol,[12] and the trial was registered with the Pan African Clinical Trials Registry (PACTR201 504000771349).

Pregnant women with singleton pregnancies were invited to participate if they had been diagnosed with preterm preeclampsia between 26+0 and 31+6 weeks gestation. The gestation at enrolment was determined by either menstrual dates (if the women was certain of her last menstrual period) or by an early or mid-trimester pregnancy ultrasound examination. Both the managing perinatologist and neonatologist had to agree that expectant management could benefit the fetus.

Women were not eligible if they had an indication for immediate delivery because they could not be treated expectantly to gain further fetal maturity. Exclusion criteria therefore included established maternal or fetal compromise that necessitated delivery, the current use or contraindications to the use of PPIs, and the use of medications that could interact with PPIs (which included warfarin, ketoconazole, voriconazole, atazanavir, nelfinavir, saquinavir, digoxin, St John's Wort, rifampin, cilostazol, diazepam, tacrolimus, erlotinib, methotrexate, and clopidogrel). Specific clinical exclusion criteria included eclampsia, severe hypertension not be controlled within 48 hours of admission, a cerebrovascular event, posterior reversible encephalopathy syndrome, severe renal impairment with a creatinine >125 μmol/L, pulmonary edema, disseminated intravascular coagulation, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, liver hematoma or rupture, severe ascites on ultrasound examination. We excluded pregnancies with a suspicion of a major fetal anomaly or malformation. Expectant management involved hospital admission with close maternal and fetal surveillance. Maternal surveillance involved 4 hourly blood pressure measurement, twice daily clinical assessments, daily urinalysis, and twice weekly biochemical testing. Fetal surveillance involved 6 hourly cardiotocography and ultrasound assessments every 2 weeks or more frequently, if indicated. To enhance fetal lung maturity, all participants received 2 doses of betamethasone that were given 24 hours apart, followed by a single repeat dose 1 week later if not delivered, as per local protocol.[13] Expectant management ended at 34 weeks gestation; women who reached this gestation were delivered. Delivery at <34 weeks gestation was a clinical decision made by the patient's treating team.

The study participants provided written informed consent. The study had Health Research Ethics Committee (HREC) approval, was approved by the South African Medicines Control Council. Study data were collected and managed with the use of REDCap electronic data capture tools.[14]

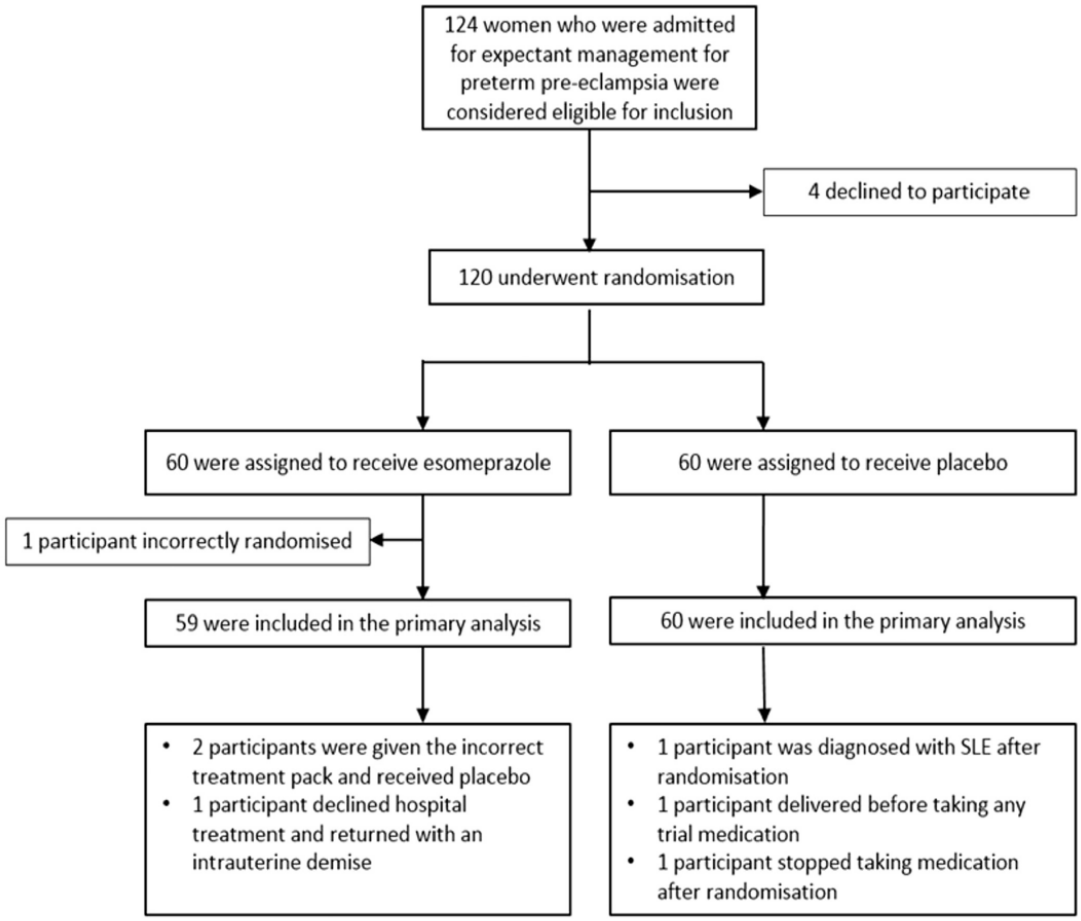
Randomization and masking

Randomization was performed in a 1:1 ratio with the use of an online, web-based sequence generator. Because gestation at randomization could possibly impact the length of pregnancy prolongation, randomization was stratified (strata 1 was ≤28+6 weeks; strata 2 was 29+0 until 31+6 weeks gestation). Randomization was done within blocks of random size within 4−6. The tablets and treatment packs were manufactured, packed, and labelled by the Institute of Drug Technology Limited (en.idtaus.com.au) in Victoria, Australia, and were identical with respect to variables such as size, thickness, physical properties, and appearance. The investigators had no access to the randomization list, and allocation concealment was maintained throughout the trial.

Placental and blood collection to measure angiogenic markers of preeclampsia and endothelial dysfunction and to perform pharmacokinetics

Plasma samples to measure circulating preeclampsia and angiogenic biomarkers were collected at randomization and twice weekly until delivery. Placental tissue

FIGURE 1
Flowchart of screening, randomization, and follow up



The flowchart summarizes the screening, randomization, allocation to esomeprazole or placebo, exclusion after randomization, complications and follow up of the study.

SLE, systemic lupus erythematosus.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

samples and umbilical artery cord blood were collected at delivery when possible. After recruitment was completed, circulating concentrations and placental expression of molecules that are markers of preeclampsia and endothelial dysfunction were measured.

Pharmacokinetics was performed in a subgroup of patients who had been administered esomeprazole. Plasma samples were drawn from a catheter in a forearm vein at the following dosing interval: predose, at 15, 30, and 45 minutes; postdose, at 1, 1.5, 2, 4, 8, and 24 hours. Levels were measured in batch after the trial was completed (the Supplemental Material provides further details on how the esomeprazole was measured).

Outcome measures

The primary outcome was prolongation of pregnancy, and the study was powered to show a prolongation of 5 days. Secondary outcomes included composite and individual maternal, fetal, and neonatal outcomes, maternal biomarkers, pharmacokinetics, and placental samples.

After completion of the trial, we measured the plasma circulating concentrations of the following markers of preeclampsia: sFlt1, soluble endoglin, placental growth factor (PlGF) with the

TABLE 1
Characteristics of trial participants at enrolment

Characteristics	Esomeprazole (n=59)	Placebo (n=60)
Gestation at randomization, wk+d		
Median [interquartile range]	29+4 [27+6–30+6]	29+5 [28+1–30+5]
Mean (standard deviation)	29.4 (1.65)	29.4 (1.66)
Gestation <29 weeks at randomization, n (%)[a]	20 (33.9)	20 (33.3)
Maternal age (y), median [interquartile range]	24 [21–31]	30 [25–34]
Body mass index (kg/m^2), median [interquartile range]	29.4 [24.8–33.3]	29.0 [24.0–35.2]
Race or ethnicity, n (%)		
Black	34 (57.6)	33 (55)
Colored (multiracial ethnic group native to Southern Africa)	25 (42.4)	27 (45.0)
Smoking, n (%)	8 (13.6)	4 (6.7)
Aspirin use, n (%)	1 (1.7)	0
Calcium use, n (%)	1 (1.7)	0
HIV positive, n (%)	8 (13.6)	12 (20.0)
Chronic hypertension, n (%)	13 (22.0)	21 (35.0)
Nulliparous, n (%)	26 (44.1)	12 (20)
Multiparous, n (%)		
Without hypertension in a previous pregnancy	25 (42.4)	27 (45)
With hypertension in a previous pregnancy	8 (13.6)	21 (34.9)
New paternity in current pregnancy, n (%)	11/37 (29.7)	17/48 (35.4)
Highest systolic blood pressure before randomization (mm Hg), mean (standard deviation)	166 (17.5)	168 (16.4)
Highest diastolic blood pressure before randomization (mm Hg), mean (standard deviation)	103 (13.4)	103 (11.4)
24-Hour protein creatinine ratio at enrolment (g/24 hr), median [interquartile range]	1.46 [0.62-3.16]	1.06 [0.57-16.86]
Hemoglobin (g/dL), mean (standard deviation)	12.3 (1.5)	11.6 (1.4)
Platelet count (10^9/L), mean (standard deviation)	207 (59.9)	222 (67.2)
Urea (mmol/L), mean (standard deviation)	4.0 (1.64)	3.7 (1.4)
Creatinine (mg/dL), mean (standard deviation)	0.05 (0.015)	0.05 (0.013)
Estimated fetal weight (g), mean (standard deviation)	1153 (300.4)	1153 (217.7)
Fetal weight percentile, median [interquartile range]	6.0 [2.1-24.8]	9.5 [1.7-22.5]
Absent blood flow on umbilical artery Doppler, n (%)	2 (3.4)	4 (6.7)

[a] Percentage of each group.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

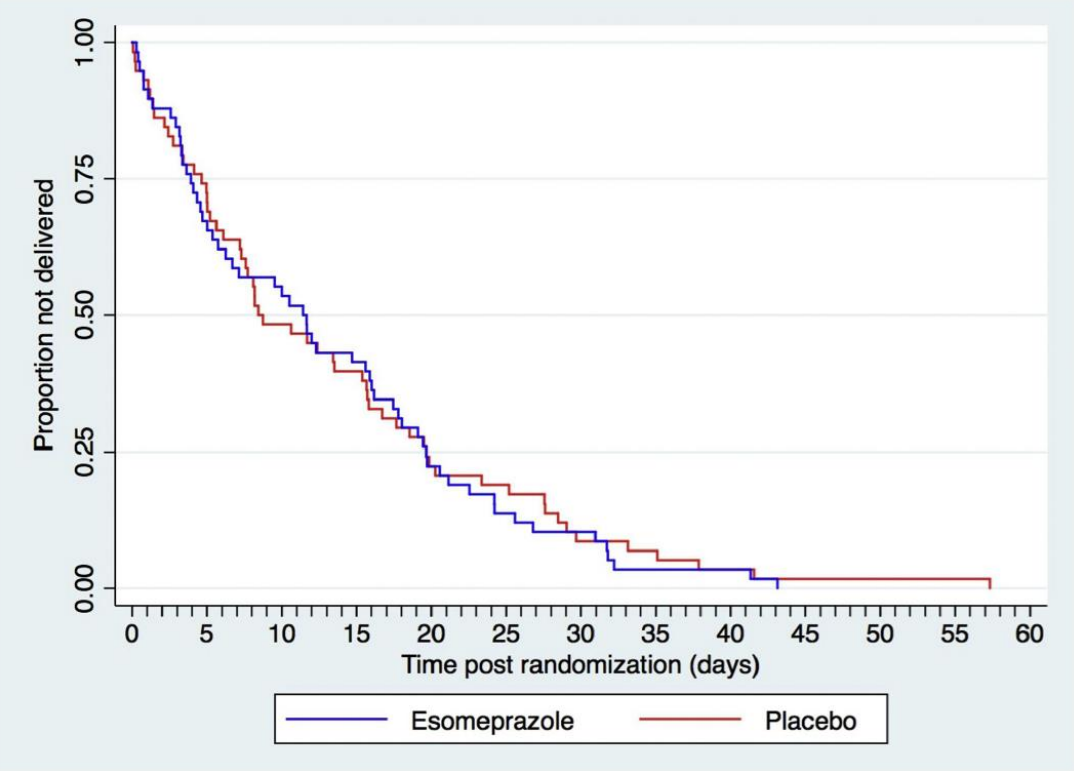
use of commercially available enzyme-linked immunosorbent assays. We also measured markers of endothelial dysfunction: endothelin-1, vascular endothelial cell adhesion molecule-1 (VCAM-1).

Total RNA was extracted from the placental biopsy specimens that were collected at delivery; the expression of sFlt1, PlGF, vascular endothelial growth factor-1, and the anti-oxidant molecule heme oxygenase-1 was measured by polymerase chain reaction (Supplemental Material).

Adherence and adverse events

Medication adherence was checked daily. After delivery, the treatment packs were collected, and the remaining tablets were counted. The trial midwife reviewed participants daily for adverse events. Serious adverse events were reported to the Data Monitoring and Safety Committee and Health Research Ethics Committee and were handled in accordance with Good Clinical Practice guidelines.

FIGURE 2
Survival curve



Survival curve shows the proportion of trial participants who remained undelivered, graphed against the number of days of gestation after randomization. *Blue* indicates the women who were treated with esomeprazole; *red* indicates the women who were treated with placebo.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

Statistical analysis

The sample size was based on data on the duration of expectant management at Tygerberg Hospital.[15] To identify a gain in gestation of 5 days, we needed to recruit 86 women (90% power, 2-sided alpha 0.05). This sample size was multiplied by 1.15 to statistically correct for non-normality. An additional 10 per arm were added to account for anticipated drop-outs. Thus, a total of 120 participants (60 per arm) had to be recruited.

Statistical analyses were performed on an intention-to-treat principle. A 2-sided *P*-value <.05 was considered to indicate statistical significance. The primary outcome was tested with the use of quantile regression analysis with the treatment group and gestational strata as covariates. Results are presented as median group difference with 95% confidence interval (95% CI). Survival analyses were done with Cox proportional hazards regression and graphed with Kaplan-Meier survivorship curves. Continuous variables were compared with either *t*-test (normally distributed variables) or Mann-Whitney *U* (nonnormally distributed data). Categoric values were compared with the use of the Fisher's exact test.

For circulating biomarker studies, between-group comparisons of circulating analyte concentrations were performed by a marginal mean model that was estimated with the use of generalized estimating equations to allow for both within patient correlation and missing samples. Graphic presentation used median, 25th, and 75th percentiles that were calculated from samples that were available at each day after random assignment. A smoothed scatterplot of these quantiles was constructed with the use of kernel-weighted local polynomial regression over a prespecified number of time units each side of the time of interest. The analysis used an Epanechnikov kernel function, automatic optimization of the degree of polynomials, and a bandwidth of 4 days.

Results

Trial participants

Participants were recruited from January 2016 until April 2017

TABLE 2
Outcomes according to trial group

Outcome	Esomeprazole (n=59)	Placebo (n=60)	*P* value
Primary			
Prolongation of gestation, d			
Median [interquartile range]	11.4 [3.6–19.7]	8.3 [3.8–19.6]	.31
Mean (standard deviation)	12.9 (10.8)	13.1(12.2)	
Gestation at delivery (wk+d), median [interquartile range]	31+2 [29+3–33+3]	31+3 [29+3–33+4]	.93
Secondary			
Composite maternal outcome, n (%)[a]	1 (1.7)	4 (6.7)	.36
Individual maternal outcomes			
Eclampsia, n (%)	0	3 (5.0)	.24
Pulmonary edema, n (%)	1 (1.7)	1 (1.7)	.99
Admission to high care unit or intensive care unit, n (%)	3 (5.1)	6 (10.0)	.49
Proteinuria ≥3g/24h, n (%)	22 (37.3)	24 (40)	.85
Systolic blood pressure >160 mm Hg, n (%)	29 (49.2)	24 (40.0)	.36
Diastolic blood pressure >110 mm Hg, n (%)	13 (22.0)	8 (13.3)	.24
Highest systolic blood pressure during trial (mm Hg), mean (standard deviation)	160 (11.9)	160 (12.3)	.91
Highest diastolic blood pressure during trial (mm Hg), mean (standard deviation)	102 (10.6)	101 (8.7)	.57
Platelet count <50×109, n (%)	0	1 (1.7)	.99
HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, n (%)	5 (8.5)	3 (5.0)	.49
Aspartate aminotransferase (level) >60 μ/L, n (%)	3 (5.1)	1 (1.7)	.30
Hemolysis (lactate dehydrogenase >600 μ/L) or hemolysis on peripheral blood smear or decreased haptoglobin, n (%)	2 (3.4)	3 (5.0)	.99
Placental abruption, n (%)	0	6 (10.0)	.03
Major postpartum hemorrhage, n (%)	0	3 (5.0)	.24
Thromboembolic disease, n (%)	1 (1.7)	0	.99
Moderate-to-severe ascites, n (%)	7 (11.9)	4 (6.7)	.36
Composite fetal outcome, n (%)[b]	49 (83.1)	45 (75)	.37
Individual fetal outcomes			
Persistent absent flow in umbilical artery Doppler, n (%)	4 (6.8)	7 (11.7)	.53
Redistribution in the middle cerebral artery, n (%)	28 (47.5)	27 (45)	.85
Growth restriction (estimated fetal weight <10th percentile), n (%)	38 (64.4)	30 (50)	.14
Significant changes in fetal heart rate pattern necessitating delivery, n (%)	28 (47.5)	26 (43.3)	.74
Intrauterine death, n (%)	1 (1.7)	1 (1.7)	.99
Neonatal composite outcome, n (%)[c]	10 (16.9)	11 (18.3)	.88

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018. (continued)

(Figure 1). Of 124 women who were admitted with preterm preeclampsia who were considered eligible, 4 women declined to participate (96.7% recruitment rate). One participant in the esomeprazole group was excluded after randomization because it was later discovered that she did not meet the trial criteria for a diagnosis of preeclampsia because she did not have significant hypertension and proteinuria. This left 59 women in the esomeprazole group. Two participants in this group were given the incorrect treatment pack and received placebo.

TABLE 2
Outcomes according to trial group *(continued)*

Outcome	Esomeprazole (n=59)	Placebo (n=60)	*P* value
Individual neonatal outcomes			
Neonatal death within 6 weeks after the due date, n (%)	7 (11.9)	9 (15.0)	.67
Grade III or IV intraventricular hemorrhage, n (%)	2 (3.4)	0	.24
Necrotizing enterocolitis, n (%)	4 (6.8)	3 (5.0)	.72
Bronchopulmonary dysplasia, n (%)	1 (1.7)	0	.50
Apgar score <7 at 5 minutes, n (%)	1 (1.7)	7 (11.7)	.06
Umbilical artery pH <7.05, n (%)	1/35 (2.9)	2/34 (5.9)	.61
Surfactant use, n (%)	14 (23.7)	9 (15.0)	.25
Neonatal intensive care unit admission, n (%)	8 (13.6)	4 (6.7)	.24
High care unit admission, n (%)	53 (89.8)	45 (75.0)	.05
Intubation and mechanical ventilation, n (%)	6 (10.2)	6 (10.0)	.99
Continuous positive airway pressure support, n (%)	46 (78.0)	39 (65.0)	.16
Grade III or IV hyaline membrane disease, n (%)	7 (11.9)	9 (15.0)	.79
Retinopathy of prematurity, n (%)	2 (3.4)	0	.24
Neonatal sepsis, n (%)	9 (15.3)	5 (8.3)	.27
Birthweight (g), mean (standard deviation)	1343 (466.5)	1379 (441.3)	.54
Discharge time (d), median [interquartile range]	3 (3–5)	3 (3–4)	.24

NOTE: No participant had any of the following outcomes: maternal death, severe renal impairment, cerebral vascular event, liver hematoma or rupture, posterior reversible encephalopathy syndrome, left ventricular failure, serum creatinine >125 μmol, disseminated intravascular coagulation, home oxygen support, persistent reversed flow in the umbilical artery Doppler.

[a] Included the occurrence of any of the following serious maternal outcomes: maternal death, eclampsia, pulmonary edema (oxygen saturation ≤90%, with clinical signs and symptoms that required treatment), severe renal impairment or the need for dialysis, a cerebral vascular event, and liver hematoma or rupture; [b] Reversed a-wave in the ductus venosus, significant changes in fetal heart rate pattern that necessitated delivery, intrauterine fetal death, fetal growth restriction, persistent reversed flow in the umbilical artery, redistribution in the middle cerebral artery Doppler, reversed a-wave in the ductus venosus Doppler; [c] Neonatal death within 6 weeks after the expected due date, grade III or IV intraventricular hemorrhage, necrotizing enterocolitis; and bronchopulmonary dysplasia.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

One participant in this group declined hospital treatment 1 week after randomization, left the hospital, and returned with a stillbirth. Sixty women were allocated to placebo, and all were included in the analysis. One participant delivered before taking her trial medication, and 1 participant was diagnosed with systemic lupus erythematosus after randomization. One participant in this group stopped taking her medication a few days before delivery. The maternal characteristics and obstetrics history of the cohort are shown in Table 1.

The median gestational age at randomization was 29 weeks 4 days in the esomeprazole group and 29 weeks 5 days in the placebo group. The placebo group had a higher median maternal age at enrolment. There were also more multiparous women, women with underlying hypertension, and women who had a previous pregnancy complicated by hypertension in the placebo group.

Primary outcome

The median time from randomization to delivery was 11.4 days (mean, 12.9 days) in the esomeprazole group vs 8.3 days (mean, 13.1 days) in the placebo group. There was no significant difference in median prolongation between treatment groups either unadjusted (median difference, 3.0; 95% CI, −2.9 to 8.8; *P*=.31) or adjusted for gestational age strata (median difference, 0.81; 95% CI, −5.1 to 6.7; *P*=.79). There was also no difference in the median prolongation between strata when adjusted for treatment group (median difference, 3.0; 95% CI, −3.2 to 9.2; *P*=.34) days.

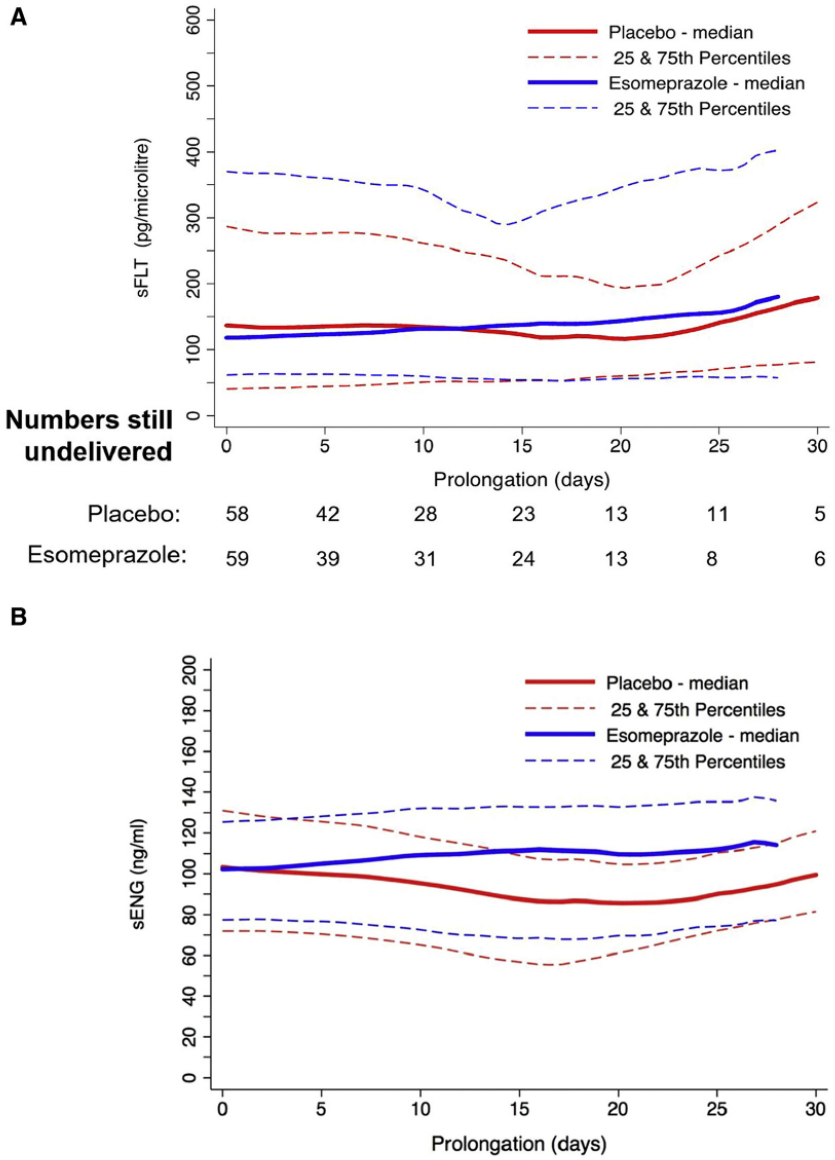
There was no difference in the instantaneous hazard of delivery, at any time, between the 2 treatment arms for either stratum (Figure 2). The estimated hazard ratio was 1.13 (95% CI, 0.70−2.17; *P*=.70) for <29 weeks and 1.07 (95% CI, 0.68−1.68; *P*=.78) for ≥29 weeks.

Secondary outcomes

There were no significant differences between treatment groups for any of the maternal, fetal, and neonatal composite or individual outcomes (Table 2), except for placental abruption. There were no placental abruptions (0/59) in the esomeprazole group and 10% (6/60) in the placebo group (*P*=.01), which was not significant when we adjusted for the fact that we performed multiple comparisons for other secondary outcomes (*P*=.14).

SFlt1 and soluble endoglin are antiangiogenic factors that are increased

FIGURE 3
Circulating plasma levels of antiangiogenic factors in women who were treated with either placebo or esomeprazole

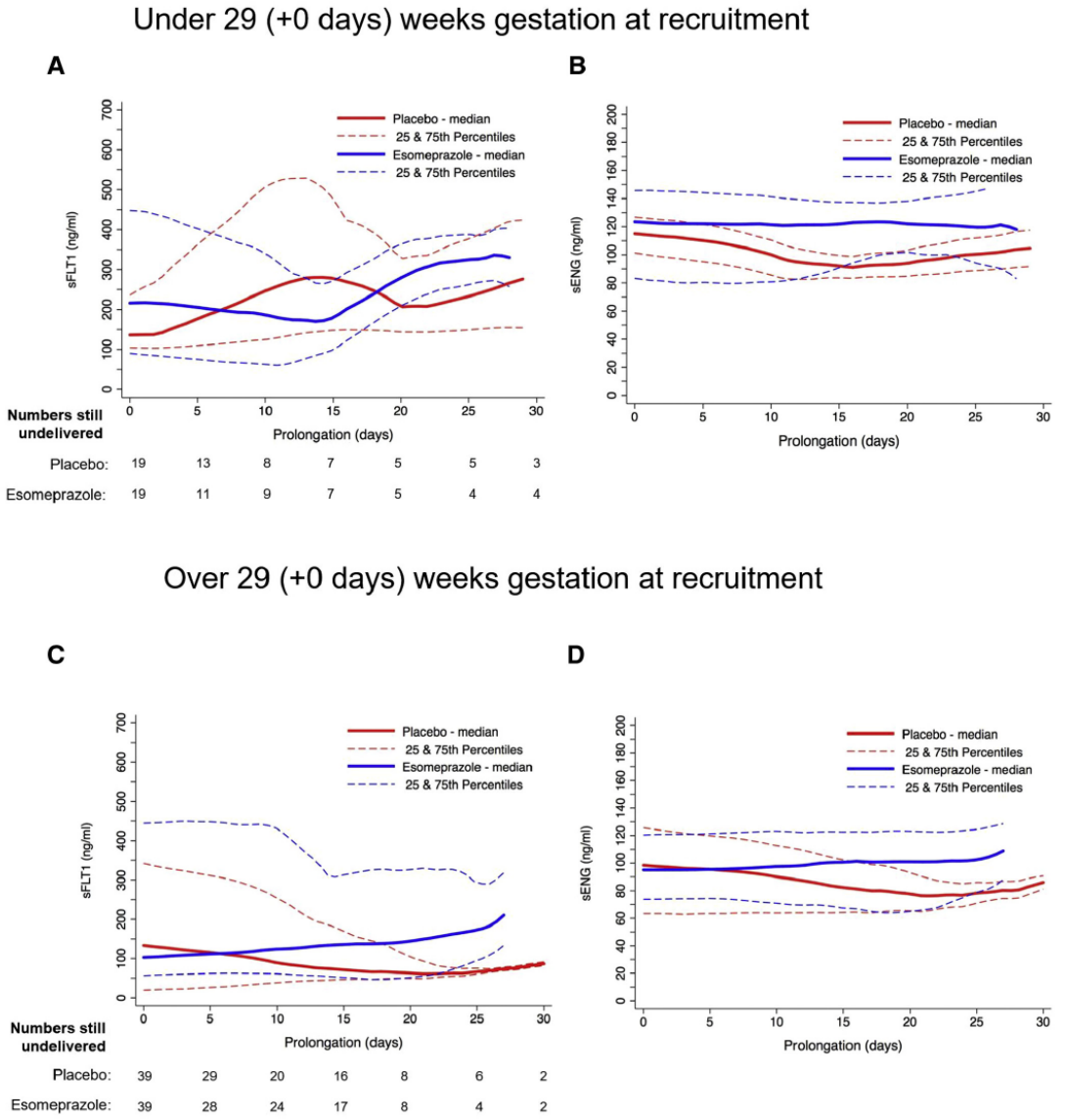


A, Median circulating plasma soluble fms-like tyrosine kinase 1 concentrations (*solid lines*) and 25th and 75th percentiles (*dotted lines*) among participants administered placebo (*red*) or esomeprazole (*blue*). There were no differences in circulating soluble fms-like tyrosine kinase 1 levels between groups. **B,** Median circulating plasma soluble endoglin concentrations (*solid line*), and 25th and 75th percentiles (*dotted line*) among participants administered placebo (*red*) or esomeprazole (*blue*). There were no differences in circulating soluble endoglin levels between groups. Numbers that were still undelivered at each 5-day time point and that could have contributed to the data for soluble fms-like tyrosine kinase 1 or soluble endoglin are shown in **A.**

sENG, soluble endoglin; *sFlt1*, soluble fms-like tyrosine kinase 1.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

FIGURE 4
Circulating plasma levels of antiangiogenic factors in women who were treated with either placebo or esomeprazole

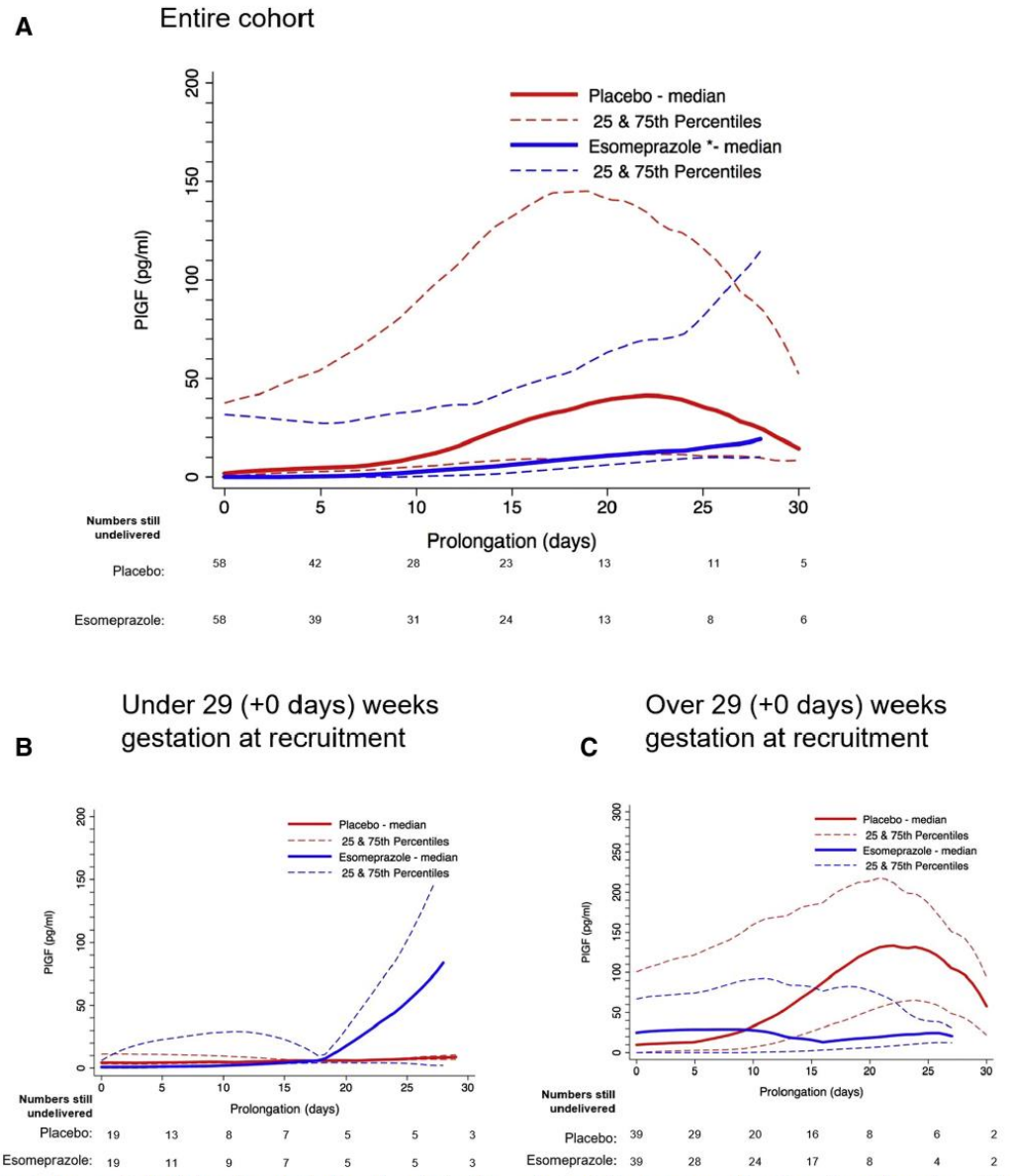


The graphs show analyte concentrations among the subcohorts of women who were either under (**A** and **B**) or over (**C** and **D**) 29 weeks gestation at recruitment. All graphs depict median circulating plasma concentrations (*solid lines*) of analytes and the 25th and 75th percentiles (*dotted lines*). None of the comparisons between esomeprazole (*blue*) and placebo (*red*) were significant. Numbers that were still undelivered at each 5-day time point and that could have contributed to the data are shown in **A** and **C** for soluble fms-like tyrosine kinase 1. The numbers that were left undelivered for soluble endoglin for **B** are the same as that shown in **A** for soluble fms-like tyrosine kinase 1; and the numbers that were left undelivered for **D** are the same as that shown in **C** for soluble fms-like tyrosine kinase 1.

sENG, soluble endoglin; *sFlt1*, soluble fms-like tyrosine kinase 1.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

FIGURE 5
Circulating plasma levels of placental growth factor in women who were treated with either placebo or esomeprazole

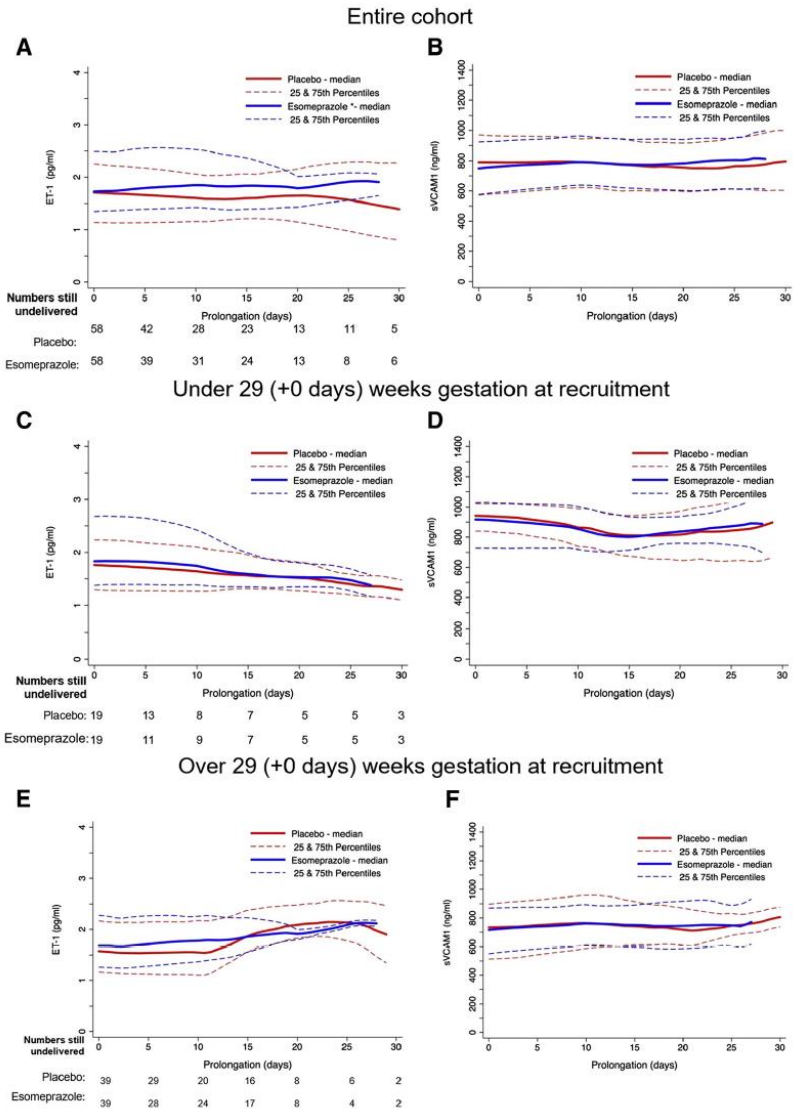


The graphs show analyte for **A**, the entire cohort or the entire cohort split according to whether women were **B**, under or **C**, over 29 weeks gestation at recruitment. All graphs depict median circulating plasma concentrations (*solid lines*) of analytes and the 25th and 75th percentiles (*dotted lines*). None of the comparisons between esomeprazole (*blue*) and placebo (*red*) were significant. Numbers that were still undelivered at each 5-day time point and could have contributed to the data are shown below each graph.

PlGF, placental growth factor.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

FIGURE 6
Circulating plasma levels of endothelin1 and soluble vascular cell adhesion molecule-1 in women who were treated with either placebo or esomeprazole

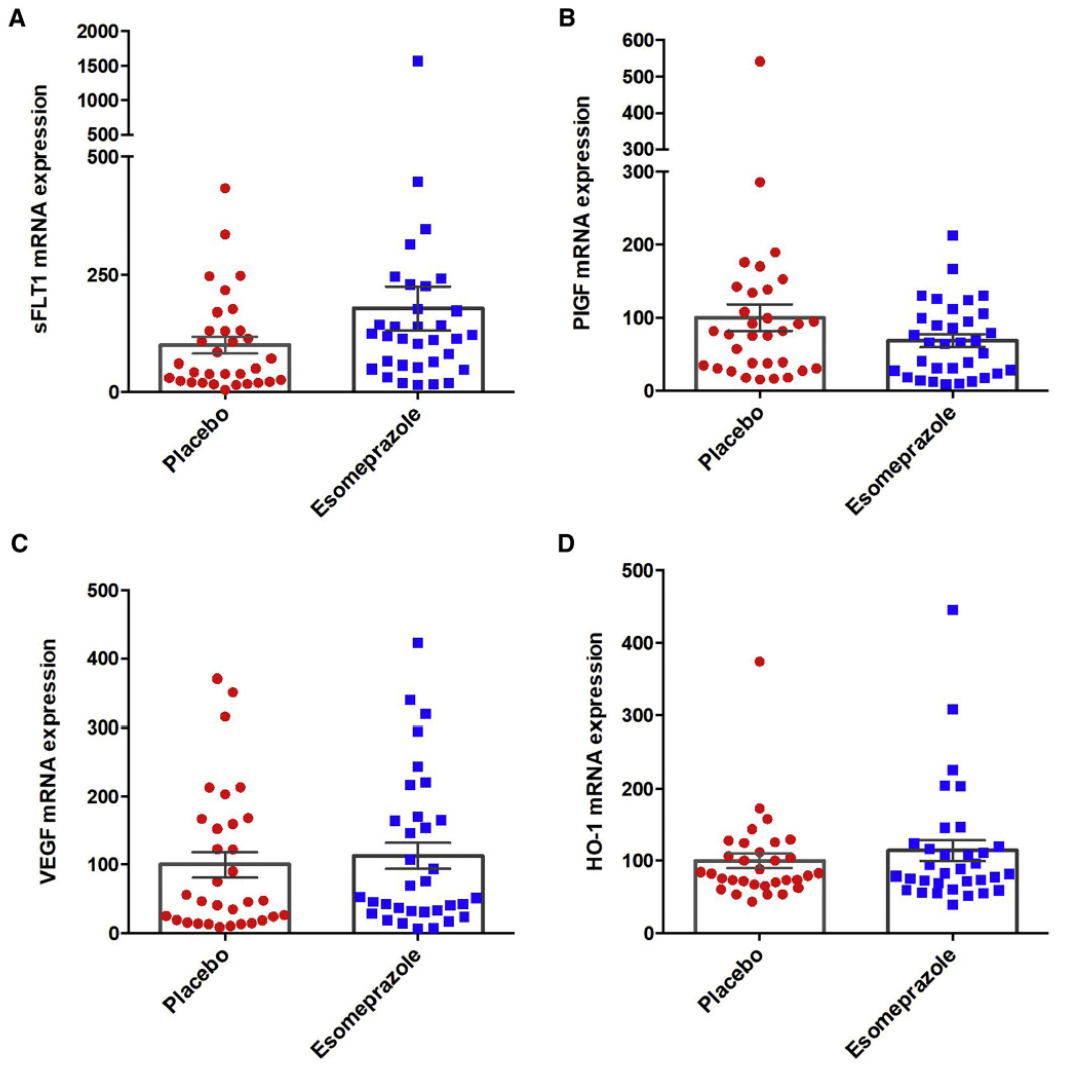


The graphs show analyte concentrations among **A** and **B**, the entire cohort or the entire cohort split according to whether women were **C** and **D**, under or **E** and **F**, over 29 weeks gestation at recruitment. All graphs depict median circulating plasma concentrations (*solid lines*) of analytes, and the 25th and 75th centiles (dotted lines). None of the comparisons between esomeprazole (*blue*) and placebo (*red*) were significant. Numbers that were still undelivered at each 5-day time point and that could have contributed to the data for **A** and **B** are shown below graph **A**; numbers that were still undelivered at each 5-day time point and that could have contributed to the data for **C** and **D** are shown below graph **C**; numbers that were still undelivered at each 5-day time point and that could have contributed to the data for **E** and **F** are shown below graph **E**.

ET-1, endothelin -1; *sVCAM1*, soluble vascular cell adhesion molecule-1.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

FIGURE 7
Placental messenger RNA expression



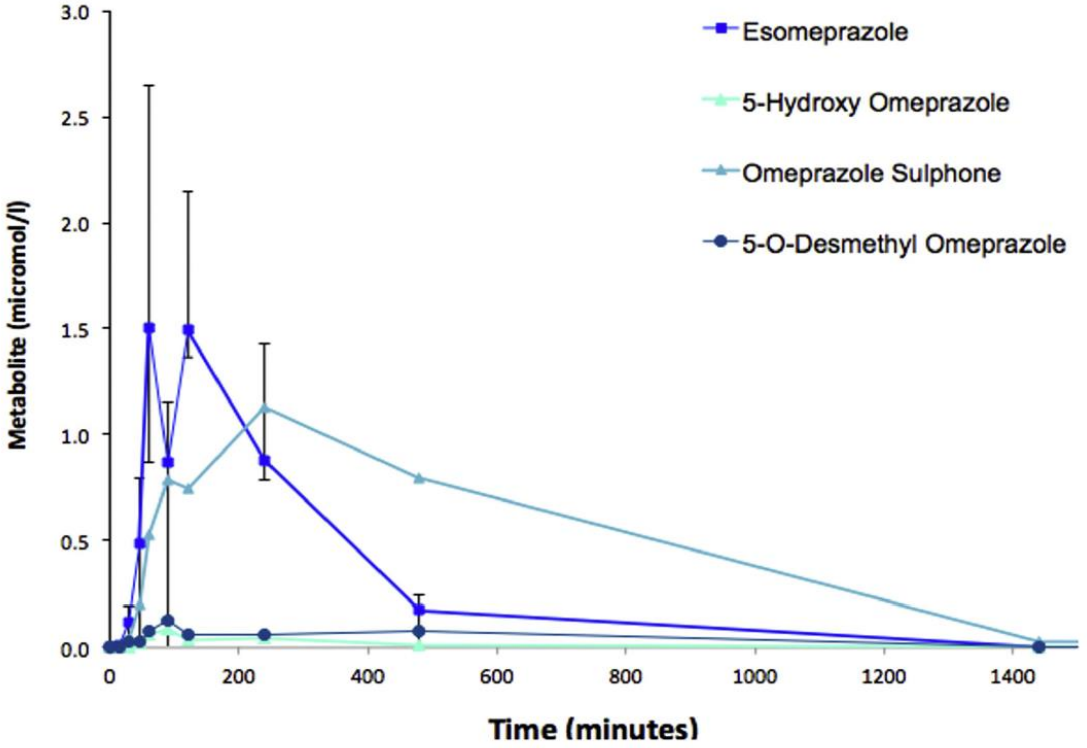
A, Soluble fms-like tyrosine kinase 1, **B**, placental growth factor, **C**, vascular endothelial growth factor, and **D**, heme oxygenase -1 in placental tissues that were collected from women who received placebo (n=32) or esomeprazole (n=33). None of the comparisons were significant. Data are mean fold change±standard error of the mean.

HO-1, heme oxygenase-1; *mRNA*, messenger RNA; *PlGF*, placental growth factor; *sFlt1*, soluble fms-like tyrosine kinase 1; *VEGF*, vascular endothelial growth factor.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

significantly in the circulation of pregnant women with preeclampsia and may have a role in the pathophysiology of the disease. Circulating sFlt1 and soluble endoglin concentrations were extremely high among trial participants, and there were no significant differences in concentrations on serial samples (which were obtained from those who were still undelivered at each time point) between the groups (Figure 3; Figure 4 shows analyte concentrations split into the 2

FIGURE 8
Pharmacokinetic analysis



Pharmacokinetic analysis showed that esomeprazole was detectable in the maternal circulation, with levels peaking soon after administration and a decline in concentration by 500 minutes after administration. Metabolites of esomeprazole (5-hydroxy, 5-O-desmethyl and omeprazole sulphone) were also detectable at lower levels soon after administration with overall higher levels of the metabolite omeprazole sulphone and a steady decrease across the first 1400 minutes.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

gestational age strata). Concentrations of both rapidly declined after delivery, as expected. There were also no differences in circulating levels of PlGF (a proangiogenic factor that is decreased in preeclampsia; Figure 5), endothelin 1 (endogenous vasoconstriction factor that is increased in preeclampsia), or vascular cell adhesion molecule-1 (associated with endothelial dysfunction; Figure 6). Analysis of placental messenger RNA expression of sFlt1, PlGF, vascular endothelial growth factor (proangiogenic factor) and heme oxygenaes-1 (endogenous antioxidant molecule) showed no differences between the esomeprazole and placebo arms (Figure 7).

Esomeprazole pharmacokinetics

Esomeprazole and its metabolites were measured in 10 participants who were assigned randomly to esomeprazole; exposure was similar to that of healthy nonpregnant volunteers with area under the curve geometric means of 5.88 μmol•h/L (95% CI, 2.96–11.68 μmol•h/L; Figure 8).[16] In contrast, esomeprazole and these metabolites were all undetectable in 9 participants who were administered placebo. Concentrations of esomeprazole and the metabolites were extremely low in the umbilical cord blood taken at birth.

Adverse events and adherence

Adherence was excellent. Only 1 participant in the placebo group stopped taking the trial medication. There were no significant differences in the incidences of serious adverse events between the 2 groups (Table 3).

Comment

In our trial, a daily dose of 40 mg of oral esomeprazole did not prolong gestation statistically further than expectant management alone. Additionally, there

TABLE 3
Severe adverse events

Adverse event	Esomeprazole (n=59), n (%)	Placebo (n=60), n (%)	*P* value
Maternal			
Eclampsia	0	3 (5)	.24
Pulmonary edema	1 (1.7)	1 (1.7)	.99
Blood loss of >1000 mL	0	3 (5)	.24
Fetal/neonatal			
Intrauterine death	1 (1.7)	1 (1.7)	.99
Neonatal death	7 (11.9)	9 (15.0)	.67
Necrotizing enterocolitis	4 (6.8)	3 (5)	.68
Neonatal sepsis	9 (15.3)	5 (8.3)	.24
Intracranial hemorrhage	2 (3.4)	0	.15

NOTE: No participant had any of the following serious adverse events: maternal death, severe renal impairment, cerebral vascular event, liver or rupture, posterior reversible encephalopathy syndrome, left ventricular failure, disseminated intravascular coagulation, fetal or neonatal congenital anomaly.

Cluver et al. Esomeprazole to treat preterm preeclampsia. Am J Obstet Gynecol 2018.

was no difference in any of the biomarker outcomes or secondary maternal, fetal, and neonatal outcomes, except for placental abruption. However, this is a secondary outcome and did not remain significant on an adjusted analysis.

Ours is only one of very few completed randomized trials to explore treatments for preterm preeclampsia. We have completed perhaps the fastest recruitment for a randomized trial of a drug treatment for preterm preeclampsia, and we achieved this at 1 site by undertaking our study in an area with a very high incidence of disease. It is also the first completed randomized treatment trial of preterm preeclampsia in which blood biomarkers of preeclampsia or endothelial dysfunction were measured, as well as placental messenger RNA expression of genes that are relevant to the pathophysiology of preeclampsia.

There was a nonsignificant trend in median prolongation in the esomeprazole group of 3 days; however, to show that such a difference is significant, we would have needed 402 participants in each arm (alpha error, 5% for 90% power; a post hoc analysis that was calculated from the actual length of gestation observed in the current trial). Despite this, there were no trends in the mean prolongation or the instantaneous hazard of delivery to support this. There was a decrease in the incidence of placental abruption, but this difference was no longer significant after we adjusted for the fact that we performed multiple comparisons for all the different secondary outcomes. Therefore, the significance of this finding, if any, is uncertain.

Esomeprazole is 97% bound to protein and 80% renally excreted. We were concerned that the significant proteinuria that often is associated with preterm preeclampsia may alter esomeprazole pharmacokinetics. Those who received esomeprazole had exposure levels similar to healthy nonpregnant volunteers that had been reported previously.[17] The esomeprazole concentrations that were observed in our participants were around the lower range of concentrations that were used in our preclinical in vitro studies.[6] Thus, although 40 mg may be an optimal dose that is effective in decreasing gastric pH,[18] it is possible that a higher dose or an intravenous dose, which has a higher exposure over time and peak concentration,[16] may be effective in treating preeclampsia.

There is now strong (though circumstantial) evidence that placental secretion of sFlt1 (which causes endothelial dysfunction) may be a significant driver of the disease.[5,19] We and others have pegged decreasing sFlt1 secretion as a strategy to treat preeclampsia.[6,20-24] We did not find changes in any of these markers, which provides biologic evidence to support our clinical findings that 40 mg of oral esomeprazole does not seem to arrest the disease course of preeclampsia once it is diagnosed.

We note that rescuing a pregnancy with advanced preterm disease with severe placental involvement may be a difficult proposition. It has been reported recently that proton inhibitor use, to combat reflux, was associated with decreased sFlt1, soluble endoglin, and endothelin-1 levels.[7] We believe it remains possible that a 40-mg dose may still have merit as a preventative treatment for preeclampsia and may be more realistic. Whether this is the case will also require clinical trials.

Esomeprazole is prescribed widely during pregnancy, and levels in the umbilical cord have not been reported previously. It was reassuring therefore that there was very little, or no, esomeprazole detected in umbilical cord blood that was sampled at birth among those who received the drug. It provides further reassurance that there is likely to be minimal fetal exposure and is consistent with epidemiologic data that show no adverse effects of PPIs on fetal development.[9-11]

There have not been many completed phase II clinical trials that have tested candidate treatments for preterm preeclampsia. Previous trials have met problems with recruitment. One of the main difficulties is that the incidence of disease is low in the developing world. Sildenafil was assessed in a single-site, double-blind randomized controlled trial in Brazil.[25] Over a 28-month period, 100 women were recruited. There was a significant prolongation of gestation in the sildenafil group of 4 days; however, given that sildenafil is a vasodilator, it is possible that this prolongation in gestation may have occurred because the drug decreased blood pressure and mitigated a clinical reason to deliver, rather than temporize disease progression. Antithrombin was assessed to treat preterm preeclampsia in the PRESERVE-1 trial

that enrolled 120 women from 23 tertiary hospitals in the United States over 28 months (ISRCTN23410175).[26] There was no difference in prolongation of pregnancy or composite neonatal outcomes.[27] Trials that have assessed serelaxin (NCT01566630), pravastatin, high doses of antithrombin,[28] and celecoxib (NCT00442676) have been attempted, but all were terminated, perhaps because of poor recruitment.

A potential limitation of our trial is that we were powered to detect a 5-day prolongation of pregnancy and therefore cannot exclude the possibility that 40 mg of esomeprazole may be effective in prolonging pregnancy by 3 days (there was a nonsignificant median difference of 3 days). However, given the findings of pharmacokinetic and biomarker studies, we are inclined to pursue further trials with higher doses rather than to repeat this same trial with a larger number of participants.

Our trial has several strengths. As noted, we performed an integrated trial in which we not only obtained data on clinical outcomes but also derived important insights by undertaking biomarker studies and pharmacokinetics that will inform our next trial. Furthermore, it was run at 1 center, which allowed us to obtain a high recruitment rate, to closely monitor compliance, and to collect uniform high-quality data. Importantly, by basing this trial at an academic center that is embedded within a population with a high incidence of preterm preeclampsia, we overcame the problem faced by previous trials of low recruitment.

In conclusion, in women with a diagnosis of preterm preeclampsia at 26−32 weeks gestation, a daily oral dose of 40 mg of esomeprazole did not prolong pregnancies. Circulating levels of sFlt1 and other antiangiogenic markers were extremely high among the cohort and were not lowered by esomeprazole. The drug appears safe and is well tolerated. In pharmacokinetic studies, we found that esomeprazole was present in the maternal circulation, but concentrations were relatively low compared with those required to elicit tissue/cell responses in our previous laboratory studies. This raises the possibility that higher doses may be effective. Reassuringly, levels of esomeprazole in the umbilical cord blood were very low, or not detectable, which provides further reassurance that very little reaches the fetal compartment.

Furthermore, we have developed and successfully completed a new protocol to evaluate drugs to treat preterm preeclampsia that embeds mechanistic insights and pharmacokinetics with clinical endpoints. We also completed recruitment in a reasonable timeframe by performing this trial in an area where the incidence of preterm preeclampsia is very high. We propose this may be an optimal approach when designing clinical trials for preterm preeclampsia. ■

Acknowledgments

We thank the members of the Data Monitoring and Safety Committee (Drs Jim Holberton, Jonathan Morris, and Lisa Yelland) and the staff at Tygerberg Hospital, Stellenbosch University, who identified participants and assisted with sample collection; Juanita Ottaway and Liddy Griffith at the South Australian Health & Medical Research for setting up and managing the offsite, online randomization sequencing; and the participants who consented to participate in this clinical trial.

References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol 2013;170:1–7.
2. Duley LM. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33:130–7.
3. Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early- onset placental dysfunction. Obstet Gynecol 2007;109:253–61.
4. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672–83.
5. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–69.
6. Onda K, Tong S, Beard S, et al. Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. Hypertension 2017;69:457–68.
7. Saleh L, Samantar R, Garrelds IM, van den Meiracker AH, Visser W, Danser AHJ. Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. Hypertension 2017;70:594–600.
8. Andersson T, Röhss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther 2001;15:1563–9.
9. Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Dig Dis Sci 2012;57:699–705.
10. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. Am J Gastroenterol 2009;104:1541–5.
11. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med 2010;363:2114–23.
12. Cluver CA, Walker SP, Mol BW, et al. Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol. BMJ Open 2015;5:e008211.
13. Hall DR. Understanding expectant management of pre-eclampsia. Obstet Gynaecol Forum 2016;26:22–7.
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
15. Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset, severe pre-eclampsia: maternal outcome. BJOG 2000;107:1252–7.
16. Hassan-Alin M, Andersson T, Bredberg E, Röhss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol 2000;56:665–70.
17. Chunduri RHB, Dannana GS. Development and validation of a high throughput UPLC–MS/MS method for simultaneous quantification of esomeprazole, rabeprazole and levosulpiride in human plasma. J Pharm Anal 2016;6:190–8.
18. Röhss K, Hasselgren G, Hedenström H. Effect of esomeprazole 40 mg vs omeprazole 40 mg on 24-hour intragastric ph in patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci 2002;47:954–8.
19. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–58.
20. Brownfoot FC, Tong S, Hannan NJ, Hastie R, Cannon P, Kaitu'u-Lino TJ. Effects of simvastatin, rosuvastatin and pravastatin on soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG) secretion from human umbilical vein endothelial cells, primary trophoblast cells and placenta. BMC Pregnancy Childbirth 2016;16:117.

21. Brownfoot FC, Hastie R, Hannan NJ, et al. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. Am J Obstet Gynecol 2016;214:356.e1–15.
22. Brownfoot FC, Tong S, Hannan NJ, et al. Effects of pravastatin on human placenta, endothelium, and women with severe preeclampsia. Hypertension 2015;66:687–97;discussion 445.
23. Hannan NJ, Brownfoot FC, Cannon P, et al. Resveratrol inhibits release of soluble fms-like tyrosine kinase (sFlt-1) and soluble endoglin and improves vascular dysfunction - implications as a preeclampsia treatment. Sci Rep 2017;7:1819.
24. Thadhani R, Kisner T, Hagmann H, et al. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation 2011;124:940–50.
25. Vigil-De Gracia P, Ludmir J. Perinatal and hemodynamic evaluation of sildenafil citrate for preeclampsia treatment. Obstet Gynecol 2016;128:1181–2.
26. Paidas MJ, Sibai BM, Triche EW, Frieling J, Lowry S; PRESERVE-1 Study Group. Exploring the role of antithrombin replacement for the treatment of preeclampsia: a prospective randomized evaluation of the safety and efficacy of recombinant antithrombin in very preterm preeclampsia (PRESERVE-1). Am J Reprod Immunol 2013;69:539–44.
27. Sibai B, Paidas MJ. LB02: randomized double-blind placebo controlled evaluation of the safety and efficacy of recombinant antithrombin vs placebo in preterm preeclampsia. Am J Obstet Gynecol 2017;216(suppl):S559–60.
28. D'Angelo A, Valsecchi L. High dose antithrombin supplementation in early preeclampsia: a randomized, double blind, placebo-controlled study. Thromb Res 2016;140:7–13.

Author and article information

From the Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, (Drs Cluver, Theron, and Hall, and Ms van Papendorp); the Division of Clinical Pharmacology, Department of Medicine, Stellenbosch University and Tygerberg Hospital (Dr Decloedt); the Division of Chemical Pathology, Stellenbosch University and National Health Laboratory Service (Dr Rensburg and Mr Schubert), Cape Town, South Africa; the Translational Obstetrics Group (Drs Cluver, Hannan, Walker, and Tong and Ms Beard), Mercy Perinatal (Drs Hannan, Walker, and Tong and Ms Beard), and the Department of Anaesthetics (Dr Hiscock), University of Melbourne, Mercy Hospital for Women, Melbourne, Victoria, Australia; the Department of Obstetrics and Gynaecology, Monash School of Medicine, Monash University, Melbourne, Victoria, Australia (Dr Mol); LCMS Central Analytical Facility and Department of Biochemistry, Stellenbosch University, Stellenbosch, South Africa (Dr Stander and Ms Adams).

Received May 7, 2018; revised July 17, 2018; accepted July 20, 2018.

Supported by The Geoff and Helen Handbury Foundation, The Beischer Medical Foundation for Mothers and Babies, The Mercy Perinatal Foundation and The Kilvington Trust; the National Health and Medical Research Foundation of Australia provided salary support to S.T. and B.W.M.; the University of Melbourne provided a CR Roper Fellowship (salary support) to N.J.H.; C.A.C. received the Discovery Academic Fellowship and the South African Medical Association PhD Bursary.

The funders had no role in the study design, the collection, analysis, and interpretation of the data, in the writing of the report, or in the decision to submit this article for publication.

This trial is registered with the Pan African Clinical Trials Registry, PACTR201 504000771349.

The authors report no conflict of interest.

Presented at the Society for Maternal-Fetal Medicine 28th Annual Pregnancy Meeting, January 29—February 3, 2018, Dallas, Texas.

Corresponding author: Catherine Anne Cluver, MMed. cathycluver@hotmail.com

Supplemental Material

Measuring plasma concentrations of esomeprazole and its metabolites

Plasma concentrations of esomeprazole and its metabolites (5-hydroxy omeprazole, omeprazole sulphone, and 5-O-desmethyl omeprazole) were determined with the use of a validated ultra-performance liquid chromatography–tandem mass spectrometry method. A Waters Acquity ultra-performance liquid chromatograph (Waters Corporation, Milford, MA) with a Waters HSS T3 column was linked to a Xevo TQ-S mass spectrometer (Waters Corporation). A gradient of 0.1% formic acid to acetonitrile was used, with d3-esomeprazole as the internal standard. In brief, the drugs were extracted with a buffered (2 mmol/L ammonium formate; pH 5.5) acetonitrile 60% solution, and the precipitated plasma proteins were separated by centrifugation (12 000*g*). The intra- and interday accuracy of the quality control samples was >90% and 85%, respectively; the intra- and interday precision was <11% and <15%, except for 5-O-desmethyl omeprazole that was 20% at the lower limit of quantification. The limit of quantitation was 1 ng/mL for all analytes. Phoenix WinNonlin software (version 9.0; Certara, Princeton, NJ) was used to characterize the pharmacokinetic parameters of esomeprazole with the use of non-compartmental analyses. The area under the plasma concentration-time curve was calculated for the 24-hr dosing interval with the log-linear trapezoidal method. Pharmacokinetic data were summarized as geometric mean values with 95% confidence intervals.

Preparation of placental tissue for analysis

Placental tissue was dissected from the whole placenta. Four pieces were dissected from distant sites; the tissue pieces were then washed in sterile phosphate-buffered saline solution, and smaller pieces were then dissected (to allow appropriate penetration of RNA preservation buffer [RNAlater]). Each piece was immersed in RNAlater according to manufacturer's instruction. Tissue samples were then blotted dry, snap frozen, and stored at −80°C until subsequent analysis.

Measuring analytes in the plasma by enzyme-linked immunosorbent assay

Patient plasma was assessed with the use of enzyme-linked immunosorbent assay for the presence of the following soluble factors: soluble Flt-1 (DuoSet VEGF R1/Flt-1 kit; R&D Systems by Bioscience, Waterloo, Australia), soluble endoglin (DuoSet Human Endoglin CD/105; R&D Systems), placental growth factor (P DuoSet PlGF; R&D Systems), endothelin-1 (Quantikine endothelin-1; R&D Systems), and soluble vascular cell adhesion molecule-1 (human VCAM-1/CD106 DuoSet; R&D Systems). Optical density for enzyme-linked immunosorbent assays was determined with a BioRad X-Mark microplate spectrophotometer (BioRad Laboratories, Inc, Hercules, CA). Protein levels were determined with BioRad Microplate Manager software (version 6; BioRad Laboratories, Inc).

Measuring expression of genes in placental tissue

Total RNA was extracted from placental tissue (from placebo [n=32] and esomeprazole [n=33] treated women) with the use of the RNeasy mini kit (Qiagen, Valencia, CA) and was quantified with a Nanodrop ND 1000 spectrophotometer (NanoDrop Technologies Inc, Wilmington, DE). RNA (0.2 μg) was converted to complementary DNA with the use of a high-capacity complementary DNA reverse transcriptase kit (Applied Biosystems Life Technologies Corporation, Carlsbad, CA), according to manufacturer guidelines.

Quantitative polymerase chain reaction was performed with the use of Taqman gene expression assays for the following genes: *sFlt1*, *HO-1*, *PlGF* and *VEGFA*. Polymerase chain reaction was performed on the CFX 384 (BioRad Laboratories, Inc) using FAM-labeled Taqman universal polymerase chain reaction mastermix (Applied Biosystems) with the following run conditions: 50°C for 2 minutes, 95°C for 10 minutes, 95°C for 15 seconds, 60°C for 1 minute (40 cycles). All data were normalized to the housekeeping genes *TOP1* and *CYC1* as an internal control and calibrated against the average cycle threshold of the control samples. The results were expressed as fold-change relative to control subjects. All samples were run in triplicate.

CHAPTER 3. The impact of coexisting fetal growth restriction on pregnancy outcomes in women undergoing expectant management for preterm preeclampsia

3.1 Overview

Early preterm preeclampsia is associated with serious complications for the mother and fetus. In well selected pregnancies, expectant management with close maternal and fetal surveillance, is established clinical practice. There are few clinical predictors that inform the likely prolongation of gestation in early preterm preeclampsia, but it might be expected that the presence of coexisting fetal growth restriction (FGR) would be an important contributor. In two previous studies,[50,51] coexisting fetal growth restriction has been associated with a shorter latency but were limited by being retrospective observational studies and provided limited data on maternal and perinatal outcome and no data on delivery outcomes. In this manuscript, a planned secondary analysis of the Preeclampsia Intervention with Esomeprazole (PIE) trial, we assessed whether antenatally diagnosed FGR influences the latency-to-delivery interval among women with preterm preeclampsia undergoing expectant management. Secondary aims were to determine if coexisting FGR influences the indication for delivery, mode of birth and the rate of maternal and perinatal complications. We defined FGR as an estimated fetal weight less than the 10th centile in this cohort.

One hundred and eighteen women were included. Two participants from the PIE trial were excluded as one did not meet the trial requirements of preeclampsia and another declined inpatient management. Sixty-eight (57.6%) had fetal growth restriction, defined as an estimated fetal weight less than the 10th

centile on ultrasound, at the time of diagnosis of preeclampsia. The latency-to-delivery interval was significantly shorter among pregnancies with coexisting fetal growth restriction compared to those without (6.5 vs 16.3 days; median difference -9.8 days (95% CI -14.6 to -5.4), P=0.0004). These pregnancies were less likely to reach 34 weeks gestation (11.8% vs 30%, P=0.01) and more likely to be delivered for suspected fetal compromise (60.3% vs 36%, P=0.01). More women with coexisting fetal growth restriction underwent an emergency caesarean section without a trial of labour induction (66.2% vs 48%, P=0.05). Of those considered eligible for induction of labour, the rate of emergency caesarean section was higher among those with fetal growth restriction (89.5% vs 60%, P=0.01). Postnatally, the presence of coexisting fetal growth restriction was associated with a higher rate of postnatal death (17.6% vs 6%, P=0.04) and necrotising enterocolitis (10.3% vs 0%, P=0.005). The rate of maternal complications did not differ between the groups.

We concluded that coexisting FGR, diagnosed at the same time as preeclampsia, is an important determinant of pregnancy outcome among women being managed expectantly for preterm preeclampsia. Coexisting FGR is associated with a shorter latency, more emergency deliveries, a lower chance of a successful induction, and increased rates of neonatal morbidity and mortality.

3.2 Manuscript

The impact of coexisting fetal growth restriction on pregnancy outcomes in women undergoing expectant management for preterm preeclampsia

Catherine A Cluver, Richard Hiscock, Erika van Papendorp, Gerhard B Theron, David R Hall, Ben Mol, Stephen Tong, Susan P Walker

ABSTRACT

Background: Preterm preeclampsia is associated with serious complications for the mother and fetus. Identifying clinical predictors of outcome would assist with counselling and management.

Objective: To assess whether the presence of fetal growth restriction (FGR) influences pregnancy latency among women with preterm preeclampsia undergoing expectant management. Secondary aims are to determine whether coexisting FGR influences the indication for delivery, mode of birth and rates of maternal and perinatal complications.

Study Design: This was a planned secondary analysis of the Preeclampsia Intervention with Esomeprazole (PIE) trial. This randomized clinical trial evaluated whether esomeprazole could prolong gestation for women diagnosed with preeclampsia between 26 and 32 weeks and considered suitable for expectant management. Delivery was indicated for deteriorating maternal or fetal status, or no later than 34 weeks. All maternal and perinatal outcomes were prospectively followed from the diagnosis of preeclampsia to six weeks after the due date. For this study, the presence of FGR (defined as an

estimated fetal weight less than the 10th centile at recruitment) was examined as a predictor of pregnancy outcome and all data were combined given the main trial yielded a negative finding.

Results: There were 118 women with preterm preeclampsia, of whom 68 (57.6%) also had co-existant FGR. Pregnancy latency was significantly shorter among pregnancies with coexisting FGR, (6.5 vs 16.3 days; median difference -9.8 days (95% CI -14.6 to -5.4), P=0.0004). These pregnancies were less likely to reach 34 weeks gestation (11.8% vs 30%, P=0.01) and more likely to be delivered for suspected fetal compromise (60.3% vs 36%.0, P=0.01). More women with FGR underwent an emergency caesarean section without a trial of labour (66.2% vs 48%, P=0.05). Of those considered eligible for induction of labour, the rate of emergency caesarean section was higher among those with FGR (89.5% vs 60%, P=0.01). The presence of coexisting FGR was associated with a higher rate of postnatal death (17.6% vs 6%, P=0.04), and necrotising enterocolitis among survivors (10.3% vs 0%, P=0.005). The rate of maternal complications did not differ between the cohorts.

Conclusion: Co-existent FGR complicates over half of women diagnosed with preterm preeclampsia and is associated with a shorter latency, more emergency caesarean deliveries, a lower probability of a successful induction, and increased rates of neonatal morbidity and mortality.

Key words: fetal growth restriction, preterm preeclampsia, pregnancy latency

Word count:

Abstract: 373

Article: 3238

INTRODUCTION

Preterm preeclampsia, occurring prior to 34 weeks gestation is associated with serious complications for both the mother and fetus.[1,2] There is currently no treatment for preeclampsia apart from delivery. This poses a serious clinical dilemma. Expectant management exposes the mother to the risks of inexorably worsening disease, yet the only alternative is delivery, with the attendant risks to the newborn of mortality and morbidity associated with preterm birth.

Around 60% of women with preterm preeclampsia may be considered suitable for expectant management, and previously studies have suggested there can be an average prolongation of gestation between 7 and 14 days.[3–5] The presence of co-existing FGR among women diagnosed with preterm preeclampsia may affect the length of gestation that may be safely gained before delivery is required. However, the degree to which this impacts on pregnancy in preterm preeclampsia has, thus far, been poorly characterized. Only two retrospective studies have examined this and both showed a shorter duration in the setting of FGR. They reported latencies among women admitted with preterm preeclampsia with FGR of 3.1 and 3 days, and without of 6.6 and 5 days, respectively.[6,7] A limitation of these findings is that they have all been obtained from retrospective data, with the Society of Maternal Fetal Medicine highlighting that this evidence gap would be best addressed with the collection of high quality prospective data.[1]

We have recently reported the results of a randomized controlled trial evaluating the effect of esomeprazole in prolonging gestation among women being managed expectantly for preterm preeclamspia (the Preeclamspia Intervention with Esomeprazole (PIE) trial). [8] . Esomeprazole did not

prolong gestation in the PIE trial, but this study provides valuable prospective data with which to assess the impact of antenatally diagnosed FGR on outcomes.

Thus, we set out to assess whether the presence of antenatally diagnosed coexisting FGR among women diagnosed with preterm preeclampsia influences pregnancy latency. We also assessed whether the presence of FGR influences the indication for delivery, the mode of birth and rates of serious adverse maternal and perinatal outcomes.

MATERIALS AND METHODS

The Preeclampsia Intervention with Esomeprazole (PIE) trial was a double blinded randomised controlled trial that recruited women with preterm preeclampsia undergoing expectant management at a single site (Tygerberg Hospital, Cape Town, South Africa) between January 2016 to April 2017 which has been published.[5,9] Women with preterm preeclampsia who did not require immediate delivery and were deemed suitable for expectant management were randomized 1:1 to 40 mg oral esomeprazole or matched placebo daily for the remainder of the pregnancy. Preterm preeclampsia was defined as a blood pressure (BP) greater than 140/90 mmHg on at least 2 occasions with proteinuria (more than 0.3 g total urinary protein excreted over a 24-hour period). Women with a singleton pregnancy with a gestational age between 26+0 and 31+6 weeks were included. Expectant management involved hospital admission with close maternal and fetal surveillance. Maternal surveillance comprised four hourly BP measurement, twice daily clinical assessments, daily urinalysis, and twice weekly biochemical testing. Fetal surveillance involved six-hourly cardiotocography and ultrasound assessments every two weeks, or more frequently if indicated. All participants received two doses of betamethasone to enhance fetal lung maturity given 24 hours apart followed by a single repeat dose one week later if not delivered. Expectant management ended at 34 weeks' gestation and women reaching this gestation were

delivered. Delivery prior to 34 weeks' gestation was a clinical decision made by the patient's treating team. Exclusion criteria included established maternal or fetal compromise mandating immediate delivery and fetuses known to have a congenital malformation. The study had approval of the Health Research Ethics Committee (HREC) and the South African Medicines Control Council. Data was collected prospectively by a research midwife and entered into a REDCap data base.[10]

To assess the impact of FGR on pregnancy latency among women recruited to PIE, we divided the study cohort according to the presence or absence of coexisting FGR diagnosed at recruitment. FGR was defined as an estimated fetal weight (EFW) below the 10th centile, using the Hadlock EFW formula derived from the head circumference, biparietal diameter, abdominal circumference and the femur length measurements and Salomon growth curves, at the time of the diagnosis of preterm preeclampsia.[11,12] All ultrasounds were performed by maternal fetal medicine specialists, trainees in maternal fetal medicine, or qualified sonographers.

Our primary outcome was prolongation of gestation which was measured from the time of recruitment until delivery. Secondary outcomes included gestational age at delivery, the indication for delivery, mode of birth, the success of induction (if performed), maternal and perinatal complications. Indications for delivery included reaching a gestational age of 34+0 weeks, suspected fetal compromise (fetal distress on antenatal nonstress test monitoring, poor fetal growth and/ or deteriorating Doppler studies on ultrasound), fetal death, placental abruption, deteriorating maternal condition, spontaneous preterm birth or if the mother declined further expectant management and requested delivery. Maternal complications included eclampsia, stroke, posterior reversible encephalopathy syndrome, death, pulmonary oedema, severe renal impairment, left ventricular failure, disseminated intravascular

coagulation, maternal admission to a high care or intensive care unit (ICU), a systolic or diastolic blood pressure greater than 160/110 mm Hg, Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, placental abruption, a major postpartum haemorrhage, thromboembolic disease and moderate to severe ascites on ultrasound. Indications for admission to a maternal high care unit include eclampsia, signs suggesting imminent eclampsia, severe pulmonary oedema requiring airway support, HELLP syndrome, blood loss requiring a massive transfusion, severe puerperal sepsis, uncontrolled hypertension requiring intravenous infusion of antihypertensive medications and placental abruption. ICU admissions were usually reserved for women requiring intubation and ventilation. Neonatal complications included neonatal death within 6 weeks of the term expected due date, grade III or IV intraventricular haemorrhage (IVH) (defined on imaging as enlarged ventricles associated with haemorrhage or when the haemorrhage extended into the cerebral tissue around the ventricles), necrotizing enterocolitis (NEC) diagnosed on radiographic studies, bronchopulmonary dysplasia (defined as needing oxygen at day 28 of life), significant neonatal sepsis as defined by the attending paediatrician, an APGAR score of less than 7 at 5 minutes, umbilical artery pH below 7.05, surfactant use, neonatal ICU or neonatal high care unit admission, intubation and mechanical ventilation or continuous positive airway pressure (CPAP) support, grade III/IV hyaline membrane disease (HMD), length of hospital stay and the incidence of retinopathy of prematurity.

The data was presented as means with standard deviations, medians with 25^{th} and 75^{th} centiles and numbers with percentages. Continuous variables were assessed using the T-Test when the data were normally distributed or a Wilcoxon rank sum if not normally distributed. Categorical variables were compared using a Chi-squared test. A P-value <0.05 or a 95% confidence interval (95%CI) not inclusive of the null value was considered to indicate statistical significance.

RESULTS

We initially recruited 120 participants to the PIE trial. They were all diagnosed with preterm preeclampsia at 26-32 weeks who were considered suitable for expectant management. One participant was later excluded as she was subsequently found to not meet the criteria for preterm preeclampsia, and another was excluded from the analysis as she withdrew from hospital care and returned with an intrauterine demise.

Of the remaining 118 participants, 68 (58%) had an EFW <10th centile at the time of recruitment, which we defined as the cohort with FGR (Fig 1). In the FGR cohort 37 had an EFW <3rd centile. The maternal and fetal characteristics are described in Table 1. Other then a lower body mass index in the FGR cohort (28 kg/ m^2 vs 32 kg/m^2, p<0.01) there were no significant differences in maternal characteristics. As expected, the EFW and fetal weight centile for gestational age were both lower in the FGR cohort (1188 g vs 1600 g, p=0.01). Absent end diastolic flow (AEDF) in the umbilical artery was present at enrolment in 6 (8.8%) of the fetuses in the FGR cohort, but in none among those with an EFW ≥10th centile.

Primary outcome

The pregnancy latency was considerably shorter among the FGR cohort (median [IQR] 6.5 [3.3 – 15.9] vs 16.3 [8.2 – 25.2] days; median difference 9.8 (95% CI -14.6 to -5.4) days, P=0.0004). Those in the FGR cohort were also less likely to reach 34 weeks gestation compared to those without FGR (11.8% vs 30%, risk difference -18.2% (95% CI -33.1 to -3.4), P=0.01). (Table 2, Fig 2)

Secondary outcomes

Indication for delivery,

Pregnancies with preterm preeclampsia and FGR were more likely to be delivered for suspected fetal compromise (60.3% vs 36%, risk difference 23.7% (95% CI 6.4 to 41.0), P=0.01) with the majority of these deliveries triggered by fetal distress on antenatal nonstress test monitoring (54.4% vs 34%, risk difference 20.4% (95% CI 2.7 to 38.1), P=0.03). There were no differences between the cohorts for other delivery indications, including deteriorating maternal condition, spontaneous preterm birth or the maternal decision to decline further expectant management (Fig 2).

Type of delivery

Women with coexisting FGR showed a trend toward a higher likelihood of undergoing emergency caesarean delivery without an attempt at inducing labour (66.2% vs 48.0%, risk difference 18.2 % (95% CI 0 to 36.0), P=0.05). The rate of emergency caesarean without induction of labour was highest among those women with an EFW <3rd centile at recruitment and was statistically significant when compared to the control cohort (73.0% vs 48.0%, risk difference 25.0% (95% CI 5.1 to 44.9), P=0.01)(Fig 3).

In the FGR cohort 19/68 had an induction of labour and 20/50 had an induction of labour in the control cohort (27.9% vs 40%, risk difference 10.3% (95% CI -29.3 to 5.2), P=0.09). In the FGR cohort only 2 inductions resulted in vaginal birth. In the control cohort there were 8 vaginal births after induction of labour (2.9% vs 16%, risk difference -13.1% (95% CI -24.0 to -2.1), P=0.01). Of the subset with an EFW <3rd centile at recruitment, significantly fewer (7/37, 18.9%) were considered suitable for induction of

labour compared to those with an EFW ≥3rd and <10th (18.9% vs 38.7%, risk difference -19.8% (95% CI -41.1 to 1.5), P=0.04) and those with EFW >10th (18.9% vs 40%, risk difference -21.1% (95% CI -39.6 to -2.5), P=0.02) (Fig 3). Notably, none of the inductions in the cohort with an EFW <3rd centile resulted in vaginal birth.

Three women (6%) in the control cohort had spontaneous preterm labour with vaginal delivery. There was no difference in the rate of elective caesarean section between cohorts.

Neonatal and maternal complications

As expected, the birthweight among infants with FGR was significantly lower than among those without coexisting FGR (1189gm vs 1600gm, mean difference 411.6gm (95% CI 261.3 to 561.8), P<0.01). There were more neonatal/infant deaths among the FGR cohort (17.6% vs 6%, risk difference 11.9% (95% CI 1.0 to 23.0), P=0.04) (Table 3 and 4). Among survivors, those with pre-existing FGR had a significantly higher rate of necrotising enterocolitis (10.3% vs 0%, risk difference 10.3% (95% CI 3.1 to 17.5), P<0.01)(Table 3).

The rate of maternal complications did not differ between the cohorts. There was a trend towards more maternal admissions to a high care or intensive care unit among pregnancies in the control cohort, but this did not achieve statistical significance (2.9% vs 12%, P=0.05, 95% CI-9.1% (-18.9 to 0.8))(Table 3).

COMMENTS

In this prospective study we confirmed that pregnancy latency is substantially shorter among women with preterm preeclampsia undergoing expectant management where there is coexisting FGR diagnosed antenataly. These women were less likely to reach 34 weeks gestation, more likely to develop fetal distress on routine antenatal nonstress test monitoring and less likely to have a successful induction of labour. The infants were more likely to have neonatal complications, including an increased risk of neonatal death.

The finding that pregnancy latency is shorter among women with preterm preeclampsia and coexisting FGR is consistent with two previous retrospective studies. Chammas et al, reported on 47 cases of preeclampsia diagnosed before 34 weeks and McKinney et al, on 199 cases of preterm preeclampsia before 37 weeks.[6,7] They reported latencies among women admitted with preterm preeclampsia with FGR of 3.1 and 3 days, and without coexisting FGR of 6.6 and 5 days, respectively. Both of these studies had considerably shorter latency than observed in our study (6.5 vs 16.3 days). This likely relates to differences in recruitment as well as timing and triggers of delivery. Chammas et al. recruited up until 34 weeks, but all pregnancies were delivered by 34 weeks. Similarly, MicKinney recruited until 37 weeks, at which point women with preeclampsia were electively delivered. These predetermined endpoints means women recruited close to this gestational age had a substantially reduced potential for latency, and delivery was less likely to be prompted by maternal or fetal indications. In contrast, we were deliberately testing an intervention to prolong gestation in preterm preeclampsia, so we prospectively ceased recruitment at 32 weeks with elective delivery deferred until 34 weeks, allowing at least 14 days of latency in all pregnancies. This provides valuable prospective data on projected latency and the effect modification of FGR. Further, both these reports were from the United States, where recourse to early

delivery can be expected to result in good neonatal outcomes. In contrast, limited access to advanced neonatal care in South Africa creates an imperative to advance gestation. Finally, the gestational age of pregnancies affected by FGR in these studies was substantially different from those that were AGA, which makes interpretation of latency more difficult. In contrast, the gestational age at recruitment in our study was very similar- 29 weeks- for both cohorts. This allowed us to more precisely map latency according to the presence or absence of FGR at the time of presentation, which is the counselling scenario facing clinicians and families.

As well as providing information regarding the likely prolongation of pregnancy, it is helpful to estimate the likely triggers for, and outcome of, planned delivery. Our finding that the presence of FGR made a fetal indication for delivery more likely is in accord with McKinney and others.[7,13,14] It is unsurprising, given that an EFW <10th centile is associated with a higher risk of underlying placental insufficiency and chronic hypoxia, circumstances where fetal decompensation is more likely. It is notable that in expectant management of preterm FGR, the presence of coexisting hypertensive disorders of pregnancy also shortens latency. The TRUFFLE trial assessed different triggers for delivery in preterm FGR, and reported that coexisting hypertensive disease significantly impacted on latency (5 vs 13 days), highlighting the impact of these dual placental pathologies on pregnancy outcome.[14]

Determining which pregnancies are likely to have a successful induction is important, given the added maternal and fetal risks associated with emergency caesarean section in preterm preeclampsia. Our study showed that the success of induction of labour with coexisting FGR is low, particularly where the EFW at diagnosis is already less than the 3rd centile. Previous studies examining the impact of FGR on induction rates in women with preterm preeclampsia have come to conflicting conclusions, but are limited by their retrospective design, and reporting by birthweight rather than fetal weight.[15–17]

Alexander et al assessed the success of induction of labour in 143 pregnancies with preterm preeclampsia with a birthweight between 750 and 1500gm, concluding that birth weight had no effect on route of delivery.[16] Similarly, Alanis et al reported on 282 women with preterm preeclampsia and concluded that induction of labour should be considered in eligible women between 28 and 34 weeks despite the presence of fetal growth restriction.[15] In contrast, Nassar reviewed the impact of antenatally diagnosed FGR on the success of induction of labour in 145 women with severe preeclampsia remote from term, reporting a trend to more caesarean sections and increased fetal distress in pregnancies with coexisting FGR. [18] The largest study to date by Roland et al, is a population based retrospective cohort of 18,296 women including women at both term and preterm gestations. They reported that coexisting FGR is associated with less successful inductions, but details on the number with preterm preeclampsia and coexisting FGR were not provided.[19] The strong influence of coesxisting FGR on induction outcome in our study may be partly situational. In order to maximise gestational age, our clinicians have a high threshold for delivery (whether for maternal or fetal indications) which likely means fetal reserves for labour are likely to be diminished.

In contrast to previous studies assessing the impact of FGR on latency in preterm preeclampsia , we have been able to provide comprehensive neonatal outcome data on all infants of mothers recruited to the PIE trial. The perinatal mortality rate of 147 per 1000 births reflects both the severity of disease, and the challenges of providing advanced neonatal care in our setting (Table 4). We found that FGR is a key determinant of neonatal mortality and morbidity, underscoring the fragile nature of severely growth restricted fetuses in the setting of preeclampsia, particularly if they are delivered before 32 weeks gestation. McKinney also reported a higher rate of perinatal mortality among infants with FGR (13.3% vs 4.4%) although data on neonatal outcome is lacking as the duration of follow up was not reported. It is notable that our perinatal mortality was dominated by neonatal deaths rather than stillbirths (15 of 16),

which reflects that high quality maternal/ fetal surveillance even among women with severe preterm disease can largely prevent antenatal stillbirth, but the postnatal risks, particularly among those with coexisting FGR, remain.

Despite the prolongation of pregnancy among women without FGR, there was no increase in maternal major morbidity. It might have been expected that the inexorable progression of preterm preeclampsia would result in more maternal complications when delivery was not mandated earlier on fetal grounds, but this was not seen. There could be several reasons for this. Firstly, pregnancies with preterm preeclampsia and coexisting FGR are likely a severe phenotype, so 'protection against maternal sequalae' are less likely. Secondly, the close inpatient maternal surveillance mandated in the PIE trial meant that maternal deterioration was detected early and delivery expedited. That there was a trend toward more maternal high care and ICU admission among the control cohort suggests that these pregnancies were managed expectantly until a maternal indication became apparent (for example, uncontrollable blood pressure or features suggesting imminent eclampsia), at which point they were aggressively managed and delivered before maternal complications resulted.

The strengths of this study are the prospective trial design which allowed us to assess the natural latency of preterm preeclampsia, and measure the impact of coexisting FGR on pregnancy outcome. This improves the quality of information with which we can manage these pregnancies and counsel affected families. We have obtained high quality prospective data on maternal and perinatal outcomes, including at the time of delivery and follow up until 6 weeks after the due date. Also, defining FGR by EFW at recruitment is pragmatic and more valuable than looking at outcomes by birthweight, and birthweight

centile, which are not useful during pregnancy. This reflects the reality of bedside counselling and decision making for women diagnosed with preterm FGR.

CONCLUSION

Antenatally diagnosed FGR is an important determinant of pregnancy outcome among women being managed expectantly for preterm preeclampsia and can assist with predicting neonatal and maternal outcomes. Coexisting FGR is associated with a shorter pregnancy latency, more emergency deliveries, a lower chance of a successful induction, and increased rates of neonatal morbidity and mortality. This prospective study provides high quality data with which to inform care in women with preterm preeclampsia with and without coexisting FGR.

REFERENCES

1 Publications Committee Society for Maternal-Fetal Medicine, Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. *Am J Obstet Gynecol* 2011; **205**: 191–8.

2 Magee LA, Yong PJ, Espinosa V, Côté AM, Chen I, von Dadelszen P. Expectant Management of Severe Preeclampsia Remote from Term: A Structured Systematic Review. *Hypertens Pregnancy* 2009; **28**: 312–47.

3 Magee L, Yong P, Chen I. Expectant Management of Severe Preeclampsia Remote from Term: A Structured Systematic Review CLIP: Community Level Interventions for Pre-eclampsia View project Community Level Intervention for Preeclampsia in Mozambique View project. 2009. DOI:10.1080/10641950802601252.

4 Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset, severe pre-eclampsia: maternal outcome. *BJOG An Int J Obstet Gynaecol* 2000; **107**: 1252–7.

5 Cluver C, Hannan N, van Papendorp E, *et al.* The Pre-eclampsia Intervention with Esomeprazole trial (PIE trial). *Am J Obstet Gynecol* 2018; **218**: S26–7.

6 Chammas MF, Nguyen TM, Li MA, Nuwayhid BS, Castro LC. Expectant management of severe preterm preeclampsia: Is intrauterine growth restriction an indication for immediate delivery? *Am J Obstet Gynecol* 2000; **183**: 853–8.

7 McKinney D, Boyd H, Langager A, Oswald M, Pfister A, Warshak CR. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. *Am J Obstet Gynecol* 2016; **214**: 395.e1-395.e7.

8 Cluver CA, Hannan NJ, van Papendorp E, *et al.* Esomeprazole to treat women with preterm

preeclampsia: a randomised placebo controlled trial. *Am J Obstet Gynecol* 2018; published online July 25. DOI:10.1016/j.ajog.2018.07.019.

9 Cluver CA, Walker SP, Mol BW, *et al.* Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol. *BMJ Open* 2015; **5**: e008211-2015-008211.

10 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377–81.

11 Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—A prospective study. *Am J Obstet Gynecol* 1985; **151**: 333–7.

12 Salomon LJ, Duyme M, Crequat J, *et al.* French fetal biometry: reference equations and comparison with other charts. *Ultrasound Obstet Gynecol* 2006; **28**: 193–8.

13 Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; **36**: 86–98.

14 Lees C, Marlow N, Arabin B, *et al.* Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013; **42**: 400–8.

15 Alanis M, Robinson C, Hulsey T, Ebeling M, Johnson D. Early-onset severe preeclampsia: induction of labor vs elective cesarean delivery and neonatal outcomes. *Am J Obstet Gynecol* 2008; **199**: 262.e1-262.e6.

16 Alexander JM, Bloom SL, McIntire DD, Leveno KJ. Severe preeclampsia and the very low birth

weight infant: is induction of labor harmful? *Obstet Gynecol* 1999; **93**: 485–8.

17 Coviello EM, Iqbal SN, Grantz KL, Huang C-C, Landy HJ, Reddy UM. Early Preterm Preeclampsia Outcomes by Intended Mode of Delivery. *Am J Obstet Gynecol* 2018; published online Sept 28. DOI:10.1016/J.AJOG.2018.09.027.

18 Nassar AH, Adra AM, Chakhtoura N, Gómez-Marín O, Beydoun S. Severe preeclampsia remote from term: labor induction or elective cesarean delivery? *Am J Obstet Gynecol* 1998; **179**: 1210–3.

19 Roland C, Warshak C, DeFranco E. Success of labor induction for pre-eclampsia at preterm and term gestational ages. *J Perinatol* 2017; **37**: 636.

TABLES

Table 1: Baseline Maternal and Fetal Characteristics at Enrolment		
Characteristics	**EFW <10th centile (n=68)**	**EFW ≥10th centile (n=50)**
Maternal characteristics		
Age in years	27 (6.5)	29 (7.0)
Body mass index (kgm^{-2})*	28 (6.6)	32 (7.5)
Race or ethnicity: Black	34 (50%)	32 (64%)
Coloured	34 (50%)	18 (36%)
Smoking	9 (13.2%)	3 (6.0%)
HIV positive n (%)	9 (13%)	11 (22%)
Chronic hypertension n (%)	18 (26.5%)	18 (36%)
Nulliparous	25 (33.8%)	15 (30%)
New paternity in current pregnancy	15 (22%)	13 (26%)
Highest systolic blood pressure before enrolment (mm Hg)	167 (18.1)	168 (11.3)
Highest diastolic blood pressure before enrolment (mm Hg)	104 (11.9)	102 (13.8)
24-hour protein creatinine ratio at enrolment (g/24 hours)	1.46 [0.61 – 3.44]	1.02 [0.56 – 2.60]
Haemoglobin (g/dl)	12.3 (1.4)	11.4 (1.4)
Platelet count ((10^{9}/L)	206 (59.4)	224 (68.3)
Urea (mmol/L)	4.1 (1.6)	3.6 (1.4)
Creatinine (mg/dL)	53 (12.3)	52 (5.1)
Randomised to esomeprazole	37 (54%)	21 (42%)
Fetal characteristics		
Gestation at enrolment	29.7 (1.4)	29.0 (1.8)
Estimated fetal weight (g) at enrollment*	1069 (217.2)	1268 (328.6)
Estimated fetal weight centile at enrollment*	2.3 [0.6 – 5.4]	26.2 [20.2 – 39.0]
Absent flow on umbilical artery Doppler at enrollment*	6 (8.8%)	0

data as mean (SD), median [25th – 75th centile] or number(%)

*significant difference between the cohorts

Table 2: Pregnancy and delivery outcomes according to EFW centile at enrolment				
	EFW<10th centile (n=68)	EFW≥10th centile (n=50)	P value*	Unadjusted 95%CI
Prolongation of pregnancy				
Median prolongation of gestation (days)	6.5 [3.3 – 15.9]	16.3 [8.2 – 25.2]	0.0004	-9.8 (-14.6 to -5.4)*
Gestation at delivery (weeks)	31.4 [29.4 – 32.9]	31.4 [29.7 – 33.9]	0.23	0.0 (-1.3 to 1.3)*
Indication for delivery of the pregnancy				
Reached 34 weeks	8 (11.8%)	15 (30%)	0.01	-18.2% (-33.1 to -3.4)
Suspected fetal compromise	41 (60.3%)	18 (36%)	0.01	23.7% (6.4 to 41.0)
Fetal death	0	1 (2%)	0.19	-2.0% (-5.9 to 1.9)
Placental abruption	1 (1.5%)	1 (2%)	0.83	0.5% (-5.4 to 4.3)
Deteriorating maternal condition	17 (25.0%)	12 (24%)	0.90	1% (-16.7 to 14.7)
Spontaneous preterm birth	0	2 (4%)	0.06	-4% (-9.4 to 1.4)
Declined further expectant management	1 (1.5%)	1 (2%)	0.83	0.5% (-5.4 to 4.3)
Type of delivery				
Emergency caesarean without induction of labour	45 (66.2%)	24 (48%)	0.05	18.2% (0 to 36.0)
Elective caesarean delivery	4 (5.9%)	3 (6%)	0.98	0.1% (-8.8 to 8.5)
Spontaneous preterm labour and vaginal delivery	0	3 (6%)	0.05	-6.0% (-12.6 to 0.0)
Successful induction	2 (2.9%)	8 (16%)	0.01	-13.1% (-24.0 to -2.1)
Failed induction with an urgent caesarean section for suspected fetal compromise	15 (22.1%)	10 (20%)	0.79	2.1% (-12.8 – 16.9)
Failed induction with nonurgent caesarean section	2 (2.9%)	2 (4%)	0.76	-1.1% (-7.8 to 5.7)

data as mean (SD), median [25th – 75th centile] or number(%)

* quantile regression used to estimate 95% CI of median.

Table 3: Neonatal and Maternal complications according to EFW centile at enrolment				
	EFW <10th centile n=68	EFW ≥10th centile n=50	P value*	Unadjusted 95%CI
Neonatal complications				
Neonatal death within 6 weeks after the due date	12 (17.6%)	3 (6%)	0.04	11.9 (1.0 to 23.0)
Grade III or IV intraventricular haemorrhage	1 (1.5%)	1 (2%)	0.82	0.5% (-5.4 to 4.3)
Necrotising enterocolitis	7 (10.3%)	0	0.005	10.3% (3.1 to 17.5)
Bronchopulmonary dysplasia	1 (1.5%)	0	0.30	1.5% (-1.4 to 4.3)
Apgar score <7 at 5 minutes	4 (5.9%)	4 (8%)	0.65	-2.1% (-11.5 to 7.3)
Umbilical artery pH <7.05	3 (4.4%)	0	0.07	4.4% (-0.5 to 9.3)
Surfactant use	14 (20.6%)	9 (18%)	0.77	2.6% (-11.8 to 16.9)
Neonatal intensive care unit admission	8 (11.8%)	4 (8%)	0.52	3.8% (-7.0 to 14.5)
High care unit admission	60 (88.2%)	38 (77.6%)	0.13	10.6% (-3.3 to 24.7)
Intubation and mechanical ventilation	9 (13.2%)	3 (6%)	0.20	7.2% (-3.2 to 17.6)
Continuous positive airway pressure support	51 (75.0%)	34 (68%)	0.50	7.0% (-9.5 to 23.5)
Grade III or IV hyaline membrane disease	8 (11.8%)	8 (16%)	0.48	-4.2 (-17.0 to 8.5)
Retinopathy of prematurity	2 (2.9%)	0	0.14	2.9% (-1.1 to 7.0)
Neonatal sepsis	8 (11.8%)	6 (12%)	0.97	-0.2% (-12.1 to 11.6)
Maternal complications				
Eclampsia	2 (2.9%)	1 (2%)	0.74	0.9% (-4.6 to 6.5)
Pulmonary oedema	1 (1.5%)	1 (2%)	0.83	0.5% (-5.4 to 4.3)
Admission to high care unit or ICU	2 (2.9%)	6 (12%)	0.05	-9.1% (-18.9 to 0.8)
Systolic blood pressure (BP) >160 mm Hg	29 (42.7)%	16 (32%)	0.24	10.7% (-6.8 to 28.1)
Diastolic BP >110 mm Hg	11 (16.2%)	6 (12%)	0.52	4.2% (-8.3 to 16.7)
Highest systolic BP during expectant management: mm Hg	161 (12.6)	157 (11.2)	0.08	4 (-8 to 1)
Highest diastolic BP during expectant management: mm Hg	102 (9.8)	102 (9.7)	0.98	0 (-4 to 4)
Highest systolic BP after delivery: mm Hg	158 (16.3)	160 (17.3)	0.43	2 (-4 to 9)
Highest diastolic BP after delivery: mm Hg	103 (13.0)	100 (10.6)	0.29	-3 (-7 to 2)
HELLP syndrome	5 (7.4%)	3 (6%)	0.77	1.4% (-7.6 to 10.7)
Placental abruption	3 (4.4%)	3 (6%)	0.70	-1.6 (-9.8 to 6.6)
Major postpartum haemorrhage	1 (1.5%)	2 (4%)	0.39	-2.5%(-8.7 to 3.6)
Thromboembolic disease	1 (1.5%)	0	0.29	1.5% (-1.4 to 4.3)
Moderate to severe ascites on ultrasound	7 (10.3%)	4 (8%)	0.67	2.3% (-8.1 to 12.7)
Blood transfusion	5 (7.4%)	3 (6%)	0.77	1.4% (-7.6 to 10.7)
Maternal discharge time (days)	3 [3 – 4]	3 [3 – 5]	0.87	0 (-0.5 to 0.5)*

data as mean (SD), median [25th – 75th centile] or number(%)

* quantile regression used to estimate 95% CI of median.

Table 4: Details on perinatal deaths							
Antenatal EFW centile	Gestation at enrollment	Gestation at delivery	Indication for delivery	Type of delivery	Weight at delivery (grams)	Age at death (days)	Neonatal complications
Intrauterine demise							
18.4	30w2d	30w3d	Placental abruption	Vaginal delivery	1460	30w3d	N /A
Neonatal and infant deaths							
EFW <10th centile							
0.1	27w5d	29w3d	Fetal distress	ECS	930	16	NEC
0.2	27w1d	27w5d	Renal deterioration	ECS	700	2	Grade IV HMD, suspected IVH
0.6	27w3d	28w2d	Fetal distress	ECS	640	1	Pulmonary haemorrhage
0.8	29w2d	29w3d	Fetal distress	ECS	1050	20	NEC
1.0	30w5d	31w3d	Deterioration in fetal Doppler studies	ECS	1400	16	Grade II HMD Found not breathing in cot Unsuccessful resus
1.0	27w5d	28w1d	Fetal distress	ECS	810	7	Grade IV HMD
3.1	27w6d	28w0d	Fetal distress	ECS	920	66	Aspirated and developed cerebral asphyxia
3.2	27w5d	28w5d	Fetal distress	ECS	1000	43	Found dead in cot
5.0	29w3d	30w1d	Low platelet count	ECS	1180	26	Aspiration
6.0	26w6d	27w6d	Fetal distress	ECS	790	50	Found dead in cot
6.4	28w5d	31w4d	Fetal distress	ECS	1060	1	Massive pulmonary haemorrhage
7.9	29w4d	31w0d	HELLP syndrome	Failed induction with ECS	1330	7	Grade IV NEC, palliative care
EFW≥10th centile							
11.6	27w4d	28w0d	Fetal distress	ECS	830	2	Grade IV HMD
19.8	26w3d	26w4d	Fetal distress	ECS	750	1	Grade IV HMD
34.1	28w3d	28w4d	Placental abruption	ECS	700	8	Grave IV HMD Suspected IVH

ECS: Emergency Caesarean Section
HMD: Hyaline Membrane Disease
IVH: Intraventricular Haemorrhage
NEC: Necrotising Enterocolitis

FIGURES

Figure 1. Flow chart of participant inclusion and exclusion

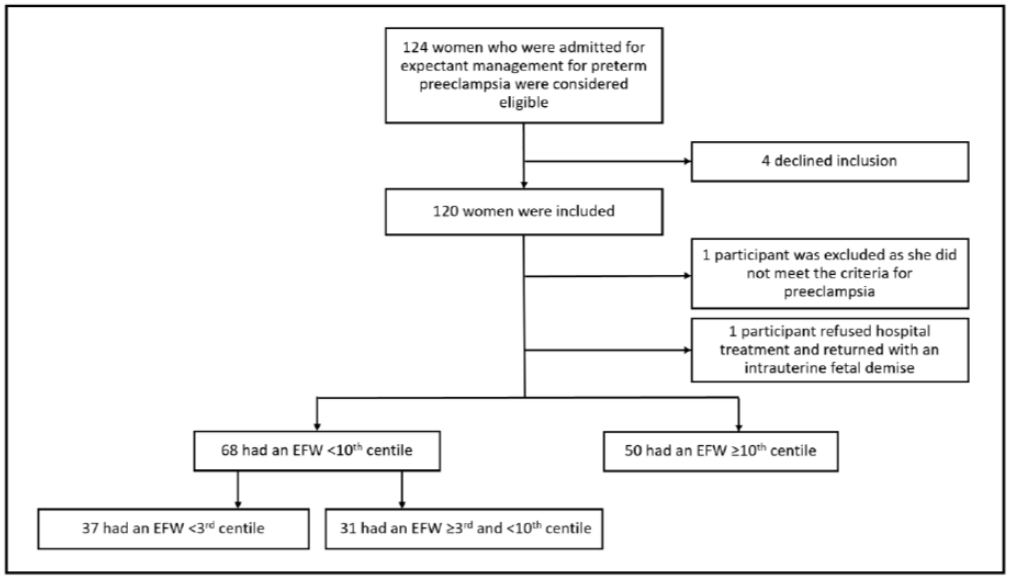
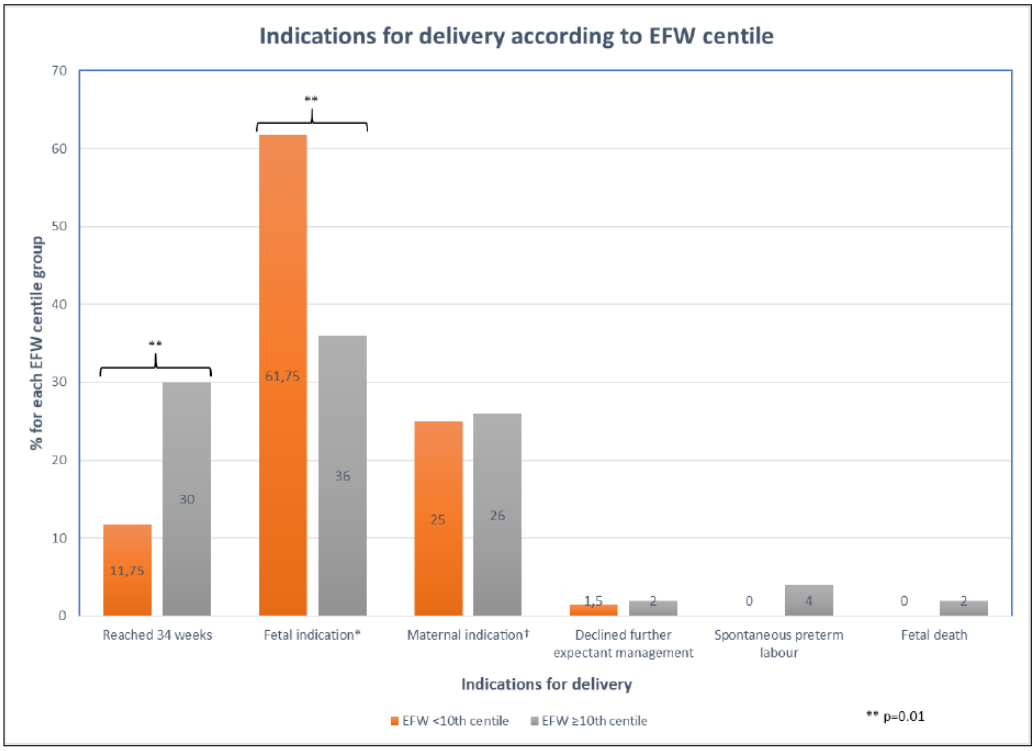


Figure 2: Graph showing the indications for delivery for the different EFW centile cohorts at inclusion



*Fetal indications included suspected fetal distress on routine antenatal nonstress test monitoring, poor fetal growth on serial ultrasounds and deteriorating Doppler studies on ultrasound

†Maternal indications for delivery included eclampsia, imminent eclampsia, HELLP syndrome, loss of blood pressure control, renal deterioration, low platelet count, severe maternal ascites, placental abruption

Figure 3: Graph depicting delivery outcomes by EFW centile at recruitment

CHAPTER 4. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

4.1 Overview

The hypertensive disorders of pregnancy contribute significantly to maternal and perinatal morbidity and mortality. Definitive treatment involves delivery at any stage of the pregnancy. For pregnancies less than 34 weeks, the risk-benefit ratio favours expectant management in well selected cases, with the aim to safely prolong gestation and improve both perinatal survival, and survival free of disability. For pregnancies between 34 weeks and term, the improvements in perinatal outcome are more modest which generates some uncertainty about the benefits and risks of a planned delivery versus expectant management.

This thesis chapter describes a Cochrane systematic review, where we aimed to assess the benefits of a planned early delivery versus a policy of expectant management in women with hypertensive disorders of pregnancy between 34 weeks and term. We only included randomised trials.

Five studies involving 1819 women were included. There was a lower risk of composite maternal morbidity and a lower risk of severe maternal morbidity for women who had a planned early delivery. There was insufficient information to draw conclusions on composite infant mortality and morbidity, but planned early delivery was associated with higher levels of respiratory distress syndrome and neonatal intensive care admissions.

Based on the limited data available, maternal outcomes appear better with planned early delivery for hypertensive disorders after 34 weeks' gestation, but it is unclear whether this is associated with increased risks for the baby, especially at earlier gestations. It was not possible to determine from the studies to date whether planned early delivery was beneficial for particular hypertensive conditions, notably preeclampsia.

Further studies are needed, preferably with reliable characterisation of hypertensive disease sub-type, to determine the ideal timing of delivery to optimise maternal and perinatal outcomes for hypertensive disorders of pregnancy occurring after 34 weeks gestation. These studies should include the maternal outcomes of mortality and severe morbidity like eclampsia, a cerebral vascular event, pulmonary oedema, severe renal impairment, a liver haematoma or rupture, liver failure, HELLP syndrome, disseminated intravascular coagulation, thromboembolic disease and placental abruption. Perinatal outcomes that should be included are fetal or neonatal death, grade III or IV intraventricular or intracerebral haemorrhage, NEC, RDS or grade III/IV, hyaline membrane disease, small-for-gestational age and neonatal seizures. The outcomes of the incidence of caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby should also be included.

An abbreviated version of the review is available in section 2.2. The full review can be found in the appendices.

4.2 Cochrane review

Cochrane Library

Cochrane Database of Systematic Reviews

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term (Review)

Cluver C, Novikova N, Koopmans CM, West HM

Cluver C, Novikova N, Koopmans CM, West HM.
Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD009273.
DOI: 10.1002/14651858.CD009273.pub2.

www.cochranelibrary.com

[Intervention Review]

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Catherine Cluver[1], Natalia Novikova[2], Corine M Koopmans[3], Helen M West[4]

[1]Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, Tygerberg, South Africa. [2]Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa. [3]Department of Obstetrics and Gynecology, University Medical Centre Groningen, Groningen, Netherlands. [4]Institute of Psychology, Health and Society, The University of Liverpool, Liverpool, UK

Contact address: Catherine Cluver, Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, PO Box 19063, Tygerberg, Western Cape, 7505, South Africa. cathycluver@hotmail.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 1, 2017.

Citation: Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD009273. DOI: 10.1002/14651858.CD009273.pub2.

ABSTRACT

Background

Hypertensive disorders in pregnancy are significant contributors to maternal and perinatal morbidity and mortality. These disorders include well-controlled chronic hypertension, gestational hypertension (pregnancy-induced hypertension) and mild pre-eclampsia. The definitive treatment for these disorders is planned early delivery and the alternative is to manage the pregnancy expectantly if severe uncontrolled hypertension is not present, with close maternal and fetal monitoring. There are benefits and risks associated with both, so it is important to establish the safest option.

Objectives

To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with hypertensive disorders, at or near term (from 34 weeks onwards).

Search methods

We searched Cochrane Pregnancy and Childbirth Trials Register (12 January 2016) and reference lists of retrieved studies.

Selection criteria

Randomised trials of a policy of planned early delivery (by induction of labour or by caesarean section) compared with a policy of delayed delivery ("expectant management") for women with hypertensive disorders from 34 weeks' gestation. Cluster-randomised trials would have been eligible for inclusion in this review, but we found none.

Studies using a quasi-randomised design are not eligible for inclusion in this review. Similarly, studies using a cross-over design are not eligible for inclusion, because they are not a suitable study design for investigating hypertensive disorders in pregnancy.

Data collection and analysis

Two review authors independently assessed eligibility and risks of bias. Two review authors independently extracted data. Data were checked for accuracy.

Main results

We included five studies (involving 1819 women) in this review.

There was a lower risk of **composite maternal mortality and severe morbidity** for women randomised to receive planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women (*evidence graded high)*). There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with lower risk of **HELLP syndrome** (RR 0.40, 95% CI 0.17 to 0.93, 1628 women; three studies) and **severe renal impairment** (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study).

There was not enough information to draw any conclusions about the effects on **composite infant mortality and severe morbidity**. We observed a high level of heterogeneity between the two studies in this analysis (two studies, 1459 infants, I^2 = 87%, Tau^2 = 0.98), so we did not pool data in meta-analysis. There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with higher levels of **respiratory distress syndrome** (RR 2.24, 95% CI 1.20 to 4.18, three studies, 1511 infants), and **NICU admission** (RR 1.65, 95% CI 1.13 to 2.40, four studies, 1585 infants).

There was no clear difference between groups for **caesarean section** (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, *evidence graded moderate)*, or in the **duration of hospital stay** for the mother after delivery of the baby (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15, two studies, 925 women, *evidence graded moderate)* or for the baby (MD -0.20 days, 95% CI -0.57 to 0.17, one study, 756 infants, *evidence graded moderate)*.

Two fairly large, well-designed trials with overall low risk of bias contributed the majority of the evidence. Other studies were at low or unclear risk of bias. No studies attempted to blind participants or clinicians to group allocation, potentially introducing bias as women and staff would have been aware of the intervention and this may have affected aspects of care and decision-making.

The level of evidence was graded high (composite maternal mortality and morbidity), moderate (caesarean section, duration of hospital stay after delivery for mother, and duration of hospital stay after delivery for baby) or low (composite infant mortality and morbidity). Where the evidence was downgraded, it was mostly because the confidence intervals were wide, crossing both the line of no effect and appreciable benefit or harm.

Authors' conclusions

For women suffering from hypertensive disorders of pregnancy after 34 weeks, planned early delivery is associated with less composite maternal morbidity and mortality. There is no clear difference in the composite outcome of infant mortality and severe morbidity; however, this is based on limited data (from two trials) assessing all hypertensive disorders as one group.

Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions. These studies should also include infant and maternal morbidity and mortality outcomes, caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby.

An individual patient meta-analysis on the data currently available would provide further information on the outcomes of the different types of hypertensive disease encountered in pregnancy.

PLAIN LANGUAGE SUMMARY

Is it safer to deliver a baby immediately or wait if the mother has high blood pressure after 34 weeks of pregnancy that is not persistently severe?

What is the issue?

Women who have high blood pressure (hypertension) during pregnancy or who develop pre-eclampsia (high blood pressure with protein in the urine or other organ systems involvement, or both) can develop serious complications. Potential complications for the mother are worsening of pre-eclampsia, development of seizures and eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), detachment of the placenta, liver failure, renal failure, and difficulty breathing because of fluid in the lungs.

Delivering the baby usually stops the mother's high blood pressure from getting worse, but a baby who is born prematurely may have other health problems, such as difficulty breathing, because the lungs are still immature. Induction of labour can lead to overstimulation of contractions and fetal distress. The alternative is waiting to deliver the baby while closely monitoring both the mother and her baby.

Why is this important?

As there are both benefits and risks to planned early delivery compared with waiting when the mother has high blood pressure toward the end of pregnancy, we wanted to know which is the safest option. We looked for clinical trials that compared planned early delivery, by induction of labour or by caesarean section, with a policy of delayed delivery of the baby.

What evidence did we find?

We searched for evidence on 12 January 2016 and found five randomised studies, involving 1819 women. Two of the studies were large, high-quality studies, in women with gestational hypertension, mild pre-eclampsia or deteriorating existing hypertension at 34 to 37 weeks (704 women) or with gestational hypertension or mild pre-eclampsia at 36 to 41 weeks (756 women). Fewer women who received planned early delivery experienced severe adverse outcomes (1459 women, *high-quality evidence*). There was not enough information to draw any conclusions about the effects on the number of babies born with poor health, with a high level of variability between the two studies (1459 infants, *low-quality evidence*). There was no clear difference between planned early delivery and delayed delivery for the number of caesarean sections (four studies, 1728 women, *moderate-quality evidence*), or the duration of the mother's hospital stay after the birth of the baby (two studies, 925 women, *moderate-quality evidence*) (or for the baby (one study, 756 infants, *moderate-quality evidence*)). More babies who were delivered early had breathing problems (respiratory distress syndrome, three studies, 1511 infants), or were admitted to the neonatal unit (four studies, 1585 infants). Fewer women who delivered early developed HELLP syndrome (three studies, 1628 women) or severe kidney problems (one study, 100 women).

Two studies compared women who had labour induced at 34 to 36 weeks and at 34 to 37 weeks with a comparison group who were monitored until 37 weeks, when induction was begun if labour had not started spontaneously. Three studies compared induction of labour at term or closer to term, at 37 completed weeks and at 36 to 41 weeks, with women who were monitored until 41 weeks when induction was begun if labour had not started spontaneously. Other inclusion and exclusion criteria also differed between the five studies.

No studies attempted to blind the women or their clinicians to which group they were in. Women and staff were aware of the intervention and this may have affected aspects of care and decision-making. Most of the evidence was of moderate quality, so we can be moderately certain about the findings.

What does this mean?

Overall, if a woman's baby was delivered immediately after 34 weeks, there was less risk of a complication for the mother and no clear difference in the overall rate of complications for the baby, but information was limited.

These findings are applicable to general obstetric practice when high blood pressure disorders during pregnancy are considered together. Further studies are needed to look at the different types of hypertensive disorders individually.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks' gestation to term

Patient or population: pregnant women with hypertensive disorders from 34 weeks' gestation to term
Setting: 2 studies in the Netherlands, 1 in India, and 1 in the USA
Intervention: planned early delivery
Comparison: expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GRADE				
Composite maternal mortality and morbidity	Study population		RR 0.69 (0.57 to 0.83)	1459 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	242 per 1000	167 per 1000 (138 to 201)				
	Moderate					
	235 per 1000	162 per 1000 (134 to 195)				
Composite infant mortality and morbidity			not pooled	1459 (2 RCTs)		This outcome was not pooled, due to substantial statistical heterogeneity (I^2 = 87%, Tau^2 = 0.98)
Caesarean section	Study population		RR 0.91 (0.78 to 1.07)	1728 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	267 per 1000	243 per 1000 (208 to 285)				
	Moderate					

	302 per 1000	275 per 1000 (236 to 324)				
Duration of hospital stay after delivery for mother (days)	The mean duration of hospital stay after delivery for mother (days) was 0	The mean duration of hospital stay after delivery for mother (days) in the intervention group was 0.16 fewer (0.46 fewer to 0.15 more)	-	925 (2 RCTs)	⊕⊕⊕○ MODERATE [1]	
Duration of hospital stay after delivery for baby (days)	The mean duration of hospital stay after delivery for baby (days) was 0	The mean duration of hospital stay after delivery for baby (days) in the intervention group was 0.2 days fewer (0.57 fewer to 0.17 more)	-	756 (1 RCT)	⊕⊕⊕○ MODERATE [1]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Wide confidence interval crossing the line of no effect.

BACKGROUND

Description of the condition

Hypertensive disorders in pregnancy are significant contributors to maternal and perinatal morbidity and mortality in low-, middle- and high-income countries (Khan 2006). They occur in up to 10% of all pregnancies (Dolea 2003; Saftlas 1990; Steegers 2010) and in up to 11% of first pregnancies (Villar 2003). There is wide variation in the incidence between different countries, and regional differences may exist (Abalos 2013). This may be explained by differences in maternal age distribution, the proportion of primiparous women among the populations (Hutcheon 2011), and dietary differences such as low-calcium intake (Belizan 1980) and genetic characteristics.

There are a number of classification systems for the hypertensive disorders of pregnancy. The most recent classification system that has been published is from the International Society for the Study of Hypertensive Disorders in Pregnancy (ISSHP) (Magee 2014). Other commonly-used classification systems are the National Institute for Health and Clinical Excellence (NICE) classification system (NICE 2010), which is currently under review, and the American College of Obstetricians and Gynecologists classification of Hypertensive disorders in pregnancy (ACOG Hypertension in Pregnancy 2013).

The ISSHP classification

Hypertension in pregnancy: office or in-hospital systolic blood pressure (BP) greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Severe hypertension: systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Pre-existing (chronic) hypertension: hypertension that predates the pregnancy or appears before 20 weeks' gestation.

Gestational hypertension: hypertension that appears at or after 20 weeks of gestation.

Pre-eclampsia: gestational hypertension and new proteinuria or one or more adverse conditions or one or more serious complications (see Table 3 for definitions of adverse conditions and serious complications).

In this classification an adverse condition consists of maternal symptoms, signs, abnormal laboratory results and abnormal fetal monitoring that may herald the development of severe maternal or fetal complications and significant proteinuria is a value greater than or equal to 0.3 g/d in a complete 24-hour urine collection or a spot (random) urine sample with greater than or equal to 30 mg/mmol urinary creatinine.

Severe pre-eclampsia: pre-eclampsia associated with a severe complication that warrants delivery regardless of gestational age.

NICE classification

Pre-existing/chronic hypertension: hypertension defined as a systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg prior to pregnancy or hypertension presenting in the first 20 weeks of pregnancy, (on at least two occasions) or hypertension persisting until at least 12 weeks postpartum or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary (essential hypertension) or secondary (to various medical conditions) in aetiology.

Gestational hypertension: elevated blood pressure (systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg measured on two occasions at least four hours apart) in previously normotensive pregnant women presenting after 20 weeks of pregnancy without proteinuria.

Severe gestational hypertension: elevated systolic blood pressure of more than 160 mmHg and/or diastolic blood pressure of more than 110 mmHg at least four hours apart.

The diagnosis of gestational hypertension is temporary and becomes pre-eclampsia if proteinuria develops, or chronic hypertension if blood pressure is still elevated at 12 weeks postpartum, or transient hypertension of pregnancy if the blood pressure is normal at 12 weeks postpartum (Magloire 2012). About 15% to 25% of women with gestational hypertension will develop pre-eclampsia (Davis 2007). This may increase up to 46% the earlier the diagnosis of gestational hypertension is made (Barton 2001).

Pre-eclampsia: hypertension (systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg) measured on two occasions at least four hours apart presenting after 20 weeks with significant proteinuria (urinary protein: creatinine ratio greater than 30 mg/mmol or more than 0.3 g in a validated 24-hour urine specimen).

Severe pre-eclampsia: pre-eclampsia with severe hypertension (systolic blood pressure above 160 mmHg and/or diastolic blood pressure above 110 mmHg) or other signs/symptoms such as symptoms of central nervous system dysfunction, liver capsule distension, liver impairment, thrombocytopenia (decrease in the number of platelets), severe proteinuria of more than 3 g in 24 hours or 3+ on dipstick, renal impairment, oliguria (less than 500 mL in 24 hours), pulmonary oedema, intrauterine growth restriction or reduced liquor volume (Duley 2009).

Pre-eclampsia superimposed on pre-existing hypertension: new onset of proteinuria after 20 weeks of pregnancy in a woman with pre-existing hypertension. In cases where proteinuria is present in early pregnancy, pre-eclampsia is defined as worsening of hypertension or development of symptoms/signs of severe pre-eclampsia (August 2012).

Complications of hypertensive disorders during pregnancy are associated with worsening of pre-eclampsia, development of eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low

platelet count), placental abruption, liver failure, renal failure, pulmonary oedema, and maternal death (Sibai 2005).

ACOG Hypertension in Pregnancy Classification

Pre-eclampsia: Blood pressure greater than or equal to 140 mmHG systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure OR a blood pressure greater than or equal to 160 mmHg systolic or greater than or equal to 110 mm Hg diastolic, confirmed within a short interval to facilitate timely antihypertensive therapy with proteinuria, defined as greater than or equal to 300 mg per 24-hour urine collection or a protein/creatinine ratio greater than or equal to 0.3 mg/dL or a dipstick reading of 1+ if other quantitative methods are not available or in the absence of proteinuria, new onset hypertension with thrombocytopaenia, renal insufficiency, impaired liver function, pulmonary oedema or cerebral or visual symptoms.
Chronic hypertension: High blood pressure known to predate conception or detected before 20 weeks of gestation.
Chronic hypertension with superimposed pre-eclampsia: Include the following scenarios:
1. Women with hypertension only in early gestation who develop proteinuria after 20 weeks of gestation.
2. Women with hypertension and proteinuria before 20 weeks who develop a sudden exacerbation of hypertension, suddenly manifest other signs and symptoms such as an increase in liver enzymes, present with thrombocytopaenia, manifest with symptoms of right upper quadrant pain and severe headaches, develop pulmonary oedema or congestion, develop renal insufficiency or have sudden substantial sustained increases in protein excretion.
Gestational hypertension: New onset hypertension after 20 weeks gestation in the absence of accompanying proteinuria.

Description of the intervention

The definitive treatment of hypertensive disorders related to pregnancy is planned early delivery. The alternative is to manage the pregnancy expectantly with close maternal and fetal monitoring. The generic Cochrane protocols on interventions for preventing (Meher 2005) and treating (Duley 2009) pre-eclampsia and its consequences cite various Cochrane Reviews covering this subject. The World Health Organization (WHO) guidelines on prevention and treatment of pre-eclampsia and eclampsia provide a summary of available evidence on various interventions (WHO 2011). There are currently no data from randomised controlled trials on interventions to monitor women with hypertensive disorders of pregnancy.
The general approach on management involves frequent blood pressure measurement, frequent assessment of maternal symptoms (headache, blurred vision, epigastric or abdominal pain, vaginal bleeding, decrease in fetal movements), urine analysis for protein with urine dipstick or ratio of protein to creatinine, and blood tests to assess renal and liver function, platelets and haemoglobin depending on the severity of the condition. For pre-eclampsia bloods are taken at least twice weekly if the maternal condition is stable or more frequently if there is any suspicion of clinical deterioration. For chronic hypertension and gestational hypertension, bloods are not routinely taken. Fetal monitoring is done by assessing fetal movements felt by the mother, fetal heart rate monitoring and fetal ultrasound (amniotic fluid measurement, fetal growth, and Doppler velocimetry in the umbilical artery, middle cerebral artery and ductus venosus) (Norwitz 2013).
Indications for delivery of women being managed expectantly would include deterioration of blood pressure control despite antihypertensive treatment, new onset maternal symptoms which include severe headache, blurred vision, epigastric or abdominal pain, vaginal bleeding and a decrease in fetal movements, deterioration in blood tests and a change in fetal condition.
Bed rest (Meher 2005), dietary salt restriction (Meher 2005), vitamin D supplementation (De Regil 2011), vitamin C and E supplementation, and thiazide diuretics are not recommended for prevention of pre-eclampsia (WHO 2011). Calcium supplementation is recommended in areas with low dietary calcium intake (Hofmeyr 2014). Low-dose aspirin, started before 16 weeks, is recommended for the prevention of pre-eclampsia in women who have risk factors for pre-eclampsia (Bujold 2014). Based on expert opinion, severe hypertension during pregnancy should be treated with antihypertensive drugs and the choice of the drug is left to the clinician managing the woman (WHO 2011).
The timing of delivery is based on the severity of the maternal condition, gestational age and fetal condition. The indications for planned early delivery (or contraindications for expectant management) include: instability of maternal condition; persistent severe hypertension unresponsive to medical therapy; persistent progressive or severe headache; visual disturbances; eclampsia; cerebrovascular events; posterior reversible encephalopathy syndrome (PRES); epigastric or abdominal pain; left ventricular failure; pulmonary oedema; severe renal impairment with a creatinine level greater than or equal to 125 μmol/l; the need for dialysis or renal failure; abruptio placenta; non-reassuring fetal testing (non-reassuring fetal heart rate tracing, estimated fetal weight less than fifth centile, oligohydramnios, persistent absent or reversed end-diastolic flow in umbilical artery Doppler); fetal demise; laboratory abnormalities (liver transaminases greater than or equal to 500 IU/L, progressive decrease in platelet count to less than 100 $\times$ 10^9/L, coagulopathy with an INR greater than 2 in the absence of an alternative cause); preterm labour; preterm premature rupture of membranes; HELLP syndrome (Norwitz 2013).
The potential implications for the mother and fetus of expectant management are weighed against the possible complications of an earlier delivery.
Traditionally, the management of hypertensive disorders in pregnancy at or near term (from 34 weeks onwards) has been a planned

early delivery by induction of labour or caesarean section. Currently, there is a tendency in high-income countries to continue with expectant management in the absence of severe pre-eclampsia past 34 0/7 gestational weeks. Canadian guidelines recommend planned early delivery after 37 0/7 weeks in case of pre-eclampsia and expectant management before 34 0/7 weeks. In case of non-severe pre-eclampsia there is insufficient evidence to recommend planned early delivery between 34 0/7 to 36 6/7 weeks (Magee 2008).

Based on a recent literature review by Spong 2011, planned early delivery is recommended:

- at 38 to 39 weeks for women with chronic hypertension on no medications;
- at 37 to 39 weeks for women with chronic hypertension controlled on medications;
- at 36 to 37 weeks for women with chronic hypertension difficult to control;
- at 37 to 38 weeks for women with gestational hypertension;
- at diagnosis for women with severe pre-eclampsia (at or after 34 weeks);
- at 37 weeks for women with mild pre-eclampsia.

How the intervention might work

Planned early delivery by induction of labour or indicated caesarean section is thought to have the following benefits:

- prevention of severe maternal complications in women with hypertensive disorders in pregnancy;
- prevention of poor fetal outcomes and stillbirth.

Potential risks of planned early delivery by induction of labour are:

- increased risk of complications associated with induction of labour such as uterine hyperstimulation and fetal distress;

Potential risks of planned early delivery by induction of labour or caesarean section are:

- concerns related to prematurity. Although the adverse outcomes due to prematurity are uncommon after 34 0/7 weeks of gestation, several recent reports have highlighted increased rates of neonatal morbidity related to respiratory distress syndrome, need for ventilation and neonatal intensive care admission when elective caesarean sections were performed before 39 0/7 weeks of gestation (Maslow 2000; Tita 2009; Wilmink 2010). Infants born between 37 0/7 and 38 6/7 weeks have greater neonatal morbidity during the first year of life in comparison with infants born between 39 0/7 and 41 0/7 weeks (Dietz 2012). Near-term infants have significantly more health problems and increased healthcare costs compared with full-term infants in the first year of life and later on (Boyle 2012; Wang 2004).

The intervention being investigated is timing of delivery. Prolonging gestation may be better for the fetus but it may increase the risks of complications for the mother.

Why it is important to do this review

There are benefits and risks associated with both policies (planned early delivery and expectant management) in women with hypertensive disorders of pregnancy. It is therefore important to establish the safest option associated with more favourable maternal and neonatal outcomes in such cases.

Management of severe pre-eclampsia before term is dealt with in another Cochrane Review comparing interventionist and expectant care (Churchill 2013).

OBJECTIVES

To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with hypertensive disorders, at or near term (from 34 weeks onwards).

METHODS

Criteria for considering studies for this review

Types of studies

We included adequately randomised controlled trials comparing planned early delivery (induction of labour or caesarean section) with expectant management of women with hypertensive disorders from 34 weeks' gestation to term. We would have included cluster-randomised trials but we found none. Studies using a quasi-randomised design are not eligible for inclusion in this review. Similarly, studies using a cross-over design are not eligible for inclusion, because they are not a suitable study design for investigating hypertensive disorders in pregnancy.

Types of participants

Women with hypertensive disorders at 34 weeks 0 days of gestation or longer.

Types of interventions

Comparison of a policy of planned early delivery (by induction of labour or by caesarean section) with a policy of delayed delivery (expectant management).

Types of outcome measures

Primary outcomes

1. Composite maternal outcome, including maternal mortality (death during pregnancy or up to 42 days after delivery) and severe morbidity (eclampsia; cerebral vascular event; pulmonary oedema as defined by trial authors; severe renal impairment, defined as a creatinine level greater than 125 μmol/l or a need for dialysis or urine output less than 0.5 mL/kg/hour for four hours unresponsive to hydration with two intravenous boluses, or as defined by trial authors; liver haematoma or rupture; liver failure, defined as the rapid impairment of synthetic function and development of encephalopathy or as defined by trial authors; haemolysis elevated liver enzymes and low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); thromboembolic disease; and abruptio placentae, defined as a retroplacental clot of more than 15% of the maternal surface or as defined by trial authors).
2. Composite perinatal outcome, including fetal or neonatal death (within six weeks after the expected due date or as defined by trial authors); grade III or IV intraventricular or intracerebral haemorrhage; necrotising enterocolitis (NEC); acute respiratory distress syndrome (ARDS) or grade III/IV hyaline membrane disease; small-for-gestational age (growth below the 10th centile or as defined by trial authors); and neonatal seizures.

Secondary outcomes

Maternal

1. Maternal mortality as described above
2. Eclampsia
3. Cerebrovascular event
4. Pulmonary oedema as defined above
5. Severe renal impairment as defined above
6. Liver haematoma or rupture*
7. Liver failure as defined above
8. HELLP syndrome
9. DIC
10. Thromboembolic disease
11. Abruptio placentae
12. Antepartum haemorrhage
13. Postpartum haemorrhage (blood loss of more than 500 mL or more within 24 hours of delivery)
14. Severe hypertension (systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than 110 mmHg)
15. Caesarean section
16. Assisted delivery (ventouse/forceps)
17. Maternal morbidity of caesarean section (wound infection, wound dehiscence, endometritis, postpartum haemorrhage (blood loss greater than 500 mL), urinary or bowel problems, venous thrombosis)
18. Maternal morbidity related to induction of labour (uterine hyperstimulation, uterine rupture, hyponatraemia, hypotension, chorioamnionitis, cord prolapse, failed induction)
19. Admission to a high care or intensive care unit*
20. Women's experiences and views on the interventions: pregnancy and childbirth experience, physical and psychological trauma, mother-infant interaction and attachment

Fetal and neonatal

1. Fetal death
2. Neonatal death as defined above
3. Grade III or IV intraventricular or intracerebral haemorrhage
4. NEC
5. ARDS or grade III/IV hyaline membrane disease
6. Small-for-gestational age as defined by trial authors
7. Neonatal seizures
8. Apgar score less than seven at five minutes
9. Cord blood pH less than 7.1 or as defined by trial authors
10. Surfactant use*
11. Neonatal intensive care unit or high care unit admission*
12. Intubation and mechanical ventilation or continuous positive airway pressure support
13. Early neonatal sepsis*

Use of health-service resources

1. Duration of hospital stay after delivery for mother
2. Duration of hospital stay after delivery for baby

Economic outcomes

1. Costs to health service resources: short-term and long-term for both mother and baby
2. Costs to the woman, her family, and society

* denotes that outcome was not specified in this review's protocol and was added at the review stage.

Search methods for identification of studies

The following Methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (1 January 2016). The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals

and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies).

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following Methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and did not need to consult a third person.

We included one study published in abstract only, as it was assessed as eligible (Majeed 2014).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion and did not need to consult a third person. We entered data into Review Manager 5 software (RevMan 2014) and checked them for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion and did not need to involve a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and are unlikely to influence the outcome; missing data have been imputed using appropriate methods);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

We assessed the quality of the evidence using the GRADE approach, as outlined in the GRADE Handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison (Planned early delivery versus expectant management (all women)):

1. Composite maternal outcome including maternal mortality (death during pregnancy or up to 42 days after delivery) and severe morbidity (eclampsia; cerebral vascular event; pulmonary oedema, as defined by trial authors; severe renal impairment, defined as a creatinine level greater than 125 μmol/l or a need for dialysis or urine output less than 0.5 mL/kg/hour for four hours unresponsive to hydration with two intravenous boluses, or as defined by trial authors; liver haematoma or rupture; liver failure, defined as the rapid impairment of synthetic function and development of encephalopathy or as defined by trial authors; haemolysis elevated liver enzymes and low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); thromboembolic disease; and abruptio placentae, defined as a retroplacental clot of more than 15% of the maternal surface or as defined by trial authors).
2. Composite perinatal outcome including fetal or neonatal death (within six weeks after the expected due date or as defined by trial authors); grade III or IV intraventricular or intracerebral haemorrhage; necrotizing enterocolitis (NEC); acute respiratory distress syndrome (ARDS) or grade III/IV hyaline membrane disease; small-for-gestational age (growth below the 10th centile or as defined by trial authors); and neonatal seizures.
3. Caesarean section.
4. Duration of hospital stay for mother after delivery.
5. Duration of hospital stay for fetus after delivery.

GRADEpro Guideline Development Tool was used to import data from Review Manager 5 (RevMan 2014) in order to create

'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes, using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as a summary risk ratio (RR) with a 95% confidence interval (CI).

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but using different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials in the analyses. If we had, we would have followed Chapter 16.3 of *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to perform analysis of cluster-randomised trials. We would have calculated the intra-cluster correlation coefficient (ICC) and design effect. We would have multiplied the standard error of the effect estimate (from analysis ignoring clustering) by the square root of the design effect. We would have performed meta-analysis using the inflate variances and the generic inverse-variance method (Chapter 16.3.6 Higgins 2011).

Cross-over trials

Cross-over trials are inappropriate for this intervention.

Multi-armed trials

We did not identify any multi-armed trials. If we had, we would have combined all relevant experimental intervention groups of the study into a single group and all relevant control intervention groups into a single control group when we analysed the data. If we had considered one of the arms irrelevant, we would have excluded it from analysis.

Dealing with missing data

For included studies, we noted levels of attrition. We did not need to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

There were fewer than 10 studies in the meta-analysis. In future updates of this review, if there are 10 or more studies in a meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager 5 software (RevMan 2014). We used a fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detected substantial statistical heterogeneity, we would have used a random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. We would have treated the random-effects summary as the average range of possible treatment effects and we would have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not combine trials.

Where we use random-effects analyses, we present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we had identified substantial heterogeneity, we would have investigated it using subgroup analyses and sensitivity analyses. We would have considered whether an overall summary is meaningful, and if it was, we would have used random-effects analysis to produce it.

We carried out the following subgroup analyses:

1. Women at 34 weeks 0 days to 36 weeks 6 days of gestation versus 37 weeks 0 days to 38 weeks 6 days versus more then 39 weeks of gestation.
2. Each gestational week.
3. Women with pre-eclampsia only versus women with gestational hypertension (mild, not severe) only or pre-existing hypertension only.

We used the following primary outcomes in subgroup analysis.

1. composite maternal
2. composite perinatal outcome

Broekhuijsen 2015 has not yet published the composite outcomes by gestational age, so we also carried out subgroup analysis using the outcome respiratory distress syndrome.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We did not need to perform sensitivity analysis for primary outcomes, as we did not identify substantial heterogeneity in the included studies.

It was not indicated to perform sensitivity analyses for aspects of the review that might affect the results; for example, where there is a risk of bias associated with the quality of some of the included trials; or to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity; and to explore the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

We would have used the following outcomes in sensitivity analyses.

1. Composite maternal outcome.
2. Composite perinatal outcome.

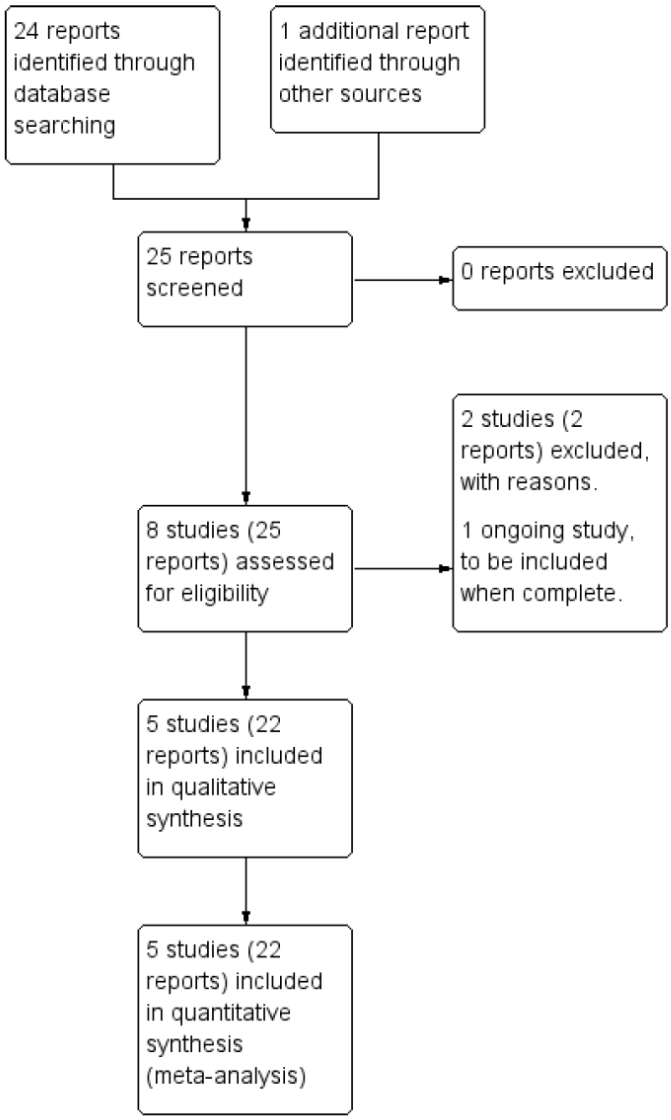
RESULTS

Description of studies

Results of the search

The search of Cochrane Pregnancy and Childbirth's Register retrieved 24 trial reports, and we found one additional report through other sources. These reports corresponded to eight studies. Five of these studies (22 reports) fulfilled the eligibility criteria for the review (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Majeed 2014; Owens 2014). Two studies (two reports) were excluded (Ramrakhyani 2001; Tukur 2007), and one study (Shennan 2013) is ongoing and will be eligible for inclusion when it is complete (*See:* Figure 1).

Figure 1. Study flow diagram.



Included studies

We included five studies (involving 1819 women) in this review (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Majeed 2014; Owens 2014). *See* Characteristics of included studies.

Design

All five of the included studies were two-arm randomised controlled trials, comparing planned early delivery with expectant management for hypertensive disorders from 34 weeks to term.

Sample sizes

Two of the studies were large multicentre trials (Broekhuijsen 2015; Koopmans 2009), which recruited 704 and 756 women respectively. Hamed 2014 recruited 76 women at two hospitals. Two studies took place in a single centre, recruiting 100 women (Majeed 2014), and 183 women (Owens 2014).

Setting

The two large multicentre trials were conducted in the Netherlands (Broekhuijsen 2015; Koopmans 2009). Three smaller studies were carried out in India (Majeed 2014), USA (Owens 2014), and Saudi Arabia and Egypt (Hamed 2014).

Participants

The gestational age ranges of women eligible for the studies were 36 to 41 weeks (Koopmans 2009), 36 to 40 weeks (Majeed 2014), 34 to 37 weeks (Broekhuijsen 2015; Owens 2014), and 24 to 36 weeks (Hamed 2014).

The type of hypertensive disorder included varied between studies: Koopmans 2009 and Majeed 2014 included pregnant women with gestational hypertension or mild pre-eclampsia, Owens 2014 included women with mild pre-eclampsia only, Broekhuijsen 2015 recruited women with gestational hypertension, mild pre-eclampsia or deteriorating chronic hypertension. Hamed 2014 was the only trial to concentrate on women with chronic hypertension (mild to moderate, without proteinuria, diagnosed before 20 weeks' gestation or if the woman was known to be hypertensive before pregnancy). Women were not eligible to participate in this study if they had gestational hypertension or new onset of pre-eclampsia where previously normotensive, in contrast to Owens 2014 and Koopmans 2009 where only women who had newly identified hypertension could participate.

Of the studies that included women with pre-eclampsia, they all excluded women with severe pre-eclampsia. Broekhuijsen 2015 and Koopmans 2009 excluded women who had a diastolic blood pressure $\geq$ 110 mmHg despite medication, a systolic blood pressure $\geq$ 170 mmHg despite medication, proteinuria $\geq$ 5 g per 24 hours, eclampsia, HELLP syndrome, pulmonary oedema or cyanosis, oliguria less than 500 mL in 24 hours, renal disease, heart disease, and severe pre-eclamptic complaints such as frontal headache or ruptured membranes. Majeed 2014 excluded women if the systolic blood pressure was above 160 mmHg, if the diastolic blood pressure was above 110 mmHg or if there was more than 5 g proteinuria per 24-hour collection. Owens 2014 excluded all that did not have mild pre-eclampsia.

Studies had different inclusion and exclusion criteria for participants, some concerning factors that may be related to, or result from, hypertensive disorders. For example, multiple pregnancies, pre-existing diabetes, and suspected intrauterine growth restriction. Broekhuijsen 2015 had the most inclusive eligibility criteria, potentially meaning that the population of women recruited to this study were more representative of women with hypertensive disorders. Multiple pregnancies were excluded from Hamed 2014, Koopmans 2009 and Owens 2014, but not excluded in Broekhuijsen 2015. In this study, 44 participants out of 703 had multifetal gestations (18 out of 352 randomised to planned early delivery, 26 out of 351 randomised to expectant monitoring), and the infant outcomes were deemed present if at least one neonate was affected. Women with diabetes mellitus were excluded from Hamed 2014, Koopmans 2009 and Owens 2014, but not excluded from Broekhuijsen 2015. Women who had a previous caesarean section were excluded from Hamed 2014 and Koopmans 2009, but not excluded from Broekhuijsen 2015. Babies with suspected intrauterine growth restriction or small-for-gestational age were excluded from Koopmans 2009 and Owens 2014, but were not excluded from Broekhuijsen 2015. Women taking antihypertensive medication were excluded from Owens 2014, excluded if the medication was intravenous in Koopmans 2009, and eligible to participate in Broekhuijsen 2015. Majeed 2014 did not describe the exclusion criteria or detailed inclusion criteria.

Interventions

Two studies compared an intervention group who had labour induced before term: at 34 to 36 weeks' gestation (Broekhuijsen 2015) and at 34 to 37 weeks (Owens 2014), with a comparison group who were monitored until 37 weeks' gestation when induction began, if labour had not started spontaneously. Three studies compared induction of labour at term or closer to term: at 37 completed weeks (Hamed 2014) and at 36 to 41 weeks (Koopmans 2009; Majeed 2014) in the intervention group, with a comparison group who were monitored until 41 weeks when induction began, if labour had not started spontaneously.

In the intervention groups, infants were delivered by induction of

labour, or by caesarean section if necessary. Three studies placed a time limit on this intervention, within 12 hours (Owens 2014) or 24 hours (Broekhuijsen 2015; Koopmans 2009) of randomisation. Labour was induced and augmented with amniotomy and oxytocin (Broekhuijsen 2015; Hamed 2014; Koopmans 2009). If necessary cervical ripening was stimulated with intracervical or intravaginal prostaglandins or a balloon catheter (Broekhuijsen 2015; Koopmans 2009) or with vaginal misoprostol (Hamed 2014).

Women in the expectant management group were monitored as outpatients (Hamed 2014), inpatients (Owens 2014), or in an inpatient or outpatient setting depending on their condition (Broekhuijsen 2015; Koopmans 2009). Monitoring consisted of measuring maternal blood pressure and screening of urine for protein (Broekhuijsen 2015; Hamed 2014; Koopmans 2009), looking for signs of disease progression with severe features of pre-eclampsia (Owens 2014), mother's assessment of fetal movements and electronic fetal heart rate monitoring (Broekhuijsen 2015; Koopmans 2009), non-stress testing (Owens 2014), and ultrasound examination (Koopmans 2009). Majeed 2014 did not provide information on the nature of the monitoring.

Outcomes

The two largest trials (Broekhuijsen 2015; Koopmans 2009) reported the composite outcome for maternal mortality and morbidity, and a composite outcome for perinatal mortality and morbidity, defined as the primary outcomes in this review. In addition, these trials reported maternal and infant mortality and morbidity outcomes individually. Maternal mortality was not reported by the other three trials (Hamed 2014; Majeed 2014; Owens 2014), and two trials did not report perinatal mortality (Majeed 2014; Owens 2014).

All studies reported on disease progression, for example, the development of severe hypertension, defined in a variety of ways (Hamed 2014; Koopmans 2009; Owens 2014), eclampsia (Broekhuijsen 2015; Koopmans 2009), HELLP syndrome (Broekhuijsen 2015; Koopmans 2009; Owens 2014), and acute renal failure (Majeed 2014). Adverse infant outcomes were reported for all trials except Majeed 2014. These include possible consequences of early delivery for the infants, such as respiratory distress syndrome (Broekhuijsen 2015; Koopmans 2009; Owens 2014), and neonatal intensive care unit admission (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Owens 2014).

Majeed 2014 was presented as a poster abstract, and the data were therefore limited. We contacted the authors for additional information, but have not received a reply. The most comprehensive reporting of outcomes was by Broekhuijsen 2015 and Koopmans 2009, with both trials presented across multiple published reports.

Funding sources

Two studies (Broekhuijsen 2015; Koopmans 2009) were funded by ZonMw, the Netherlands Organisation for Health Research and Development. Hamed 2014 and Owens 2014 were both funded through their affiliated universities: Qassim University and the University of Mississippi Medical Centre, respectively. As Majeed 2014 was presented as a poster abstract, with limited information given, it is not clear who provided funding for this study.

Declarations of interest

None of the study authors declared any conflicts of interest. This was not mentioned in Majeed 2014.

Excluded studies

We excluded two studies (two reports); one because it was not a randomised controlled trial, with group allocation based on gestational age at presentation (Ramrakhyani 2001), and the other compared two methods of planned early delivery: caesarean section and induction with vaginal misoprostol (Tukur 2007). See Characteristics of excluded studies.

Ongoing studies

We found one ongoing study (Shennan 2013). This trial compares planned early delivery with monitoring until induction at 37 weeks' gestation, for pregnant women with pre-eclampsia between 34 and 37 weeks of gestation. According to the protocol, recruitment started in April 2014, and it was anticipated that it will take approximately three years to recruit 900 women. See Characteristics of ongoing studies.

Risk of bias in included studies

Assessment of the methodological quality of the included studies was based on risk of bias in relation to selection bias (method of randomisation and allocation concealment), performance bias, detection bias, attrition bias (loss of participants from the analyses) and reporting bias. A summary of 'Risk of bias' assessments for each study, and for included trials overall, are set out in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

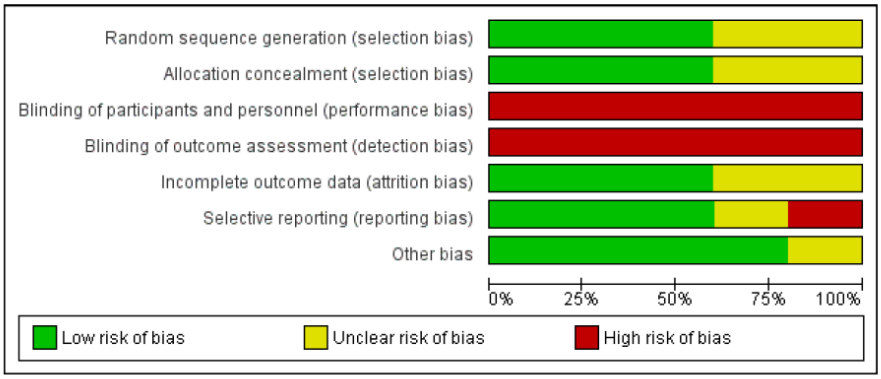
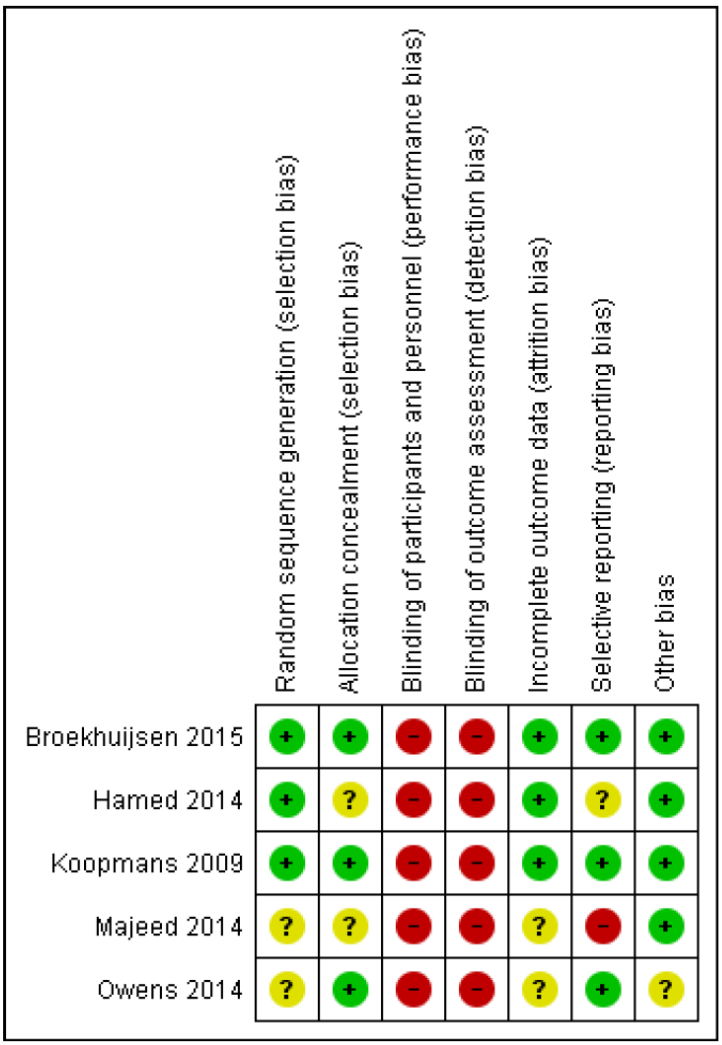


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of the randomisation sequence

Three studies reported using a computerised or web-based random-number generator to generate the randomisation sequence, which we judged were at low risk of bias (Broekhuijsen 2015; Hamed 2014; Koopmans 2009). We judged the remaining two studies to be at unclear risk of bias: Owens 2014 described using stratified and random permuted blocks of two but did not describe how the randomisation sequence was generated, and Majeed 2014 did not mention the method for determining the randomisation sequence.

Allocation concealment

In two of the studies, the method for concealing group allocation at the point of randomisation was not clear (Hamed 2014; Majeed 2014). Three studies were at low risk of bias: Owens 2014 concealed allocation in sealed envelopes, and the web-based central allocation of Broekhuijsen 2015 and Koopmans 2009 concealed their allocation.

Blinding

The blinding of women and health professionals was not possible for this intervention. This may have had an effect on other treatment decisions. All included studies have consequently been assessed as high risk of bias due to lack of blinding.

Incomplete outcome data

We considered the risk of bias to be low in Broekhuijsen 2015, Hamed 2014 and Koopmans 2009, as all women were accounted for and there was little or no attrition. The number of women allocated to each group was not reported by Majeed 2014, so we judged the risk of bias to be unclear as we cannot assess whether data for all women are reported. There was some attrition from Owens 2014, and the data were not presented as intention-to-treat, so we considered that the risk of bias is also unclear for this trial.

Selective reporting

Protocols were available for Broekhuijsen 2015, Koopmans 2009 and Owens 2014. All prespecified outcomes were reported for these trials, so we judged these to be at a low risk of reporting bias. Reporting appeared to be good in Hamed 2014, however no protocol was available to assess whether all prespecified outcomes were reported, so risk of bias was unclear. Majeed 2014 was assessed from a poster-presentation abstract, which only reported significant findings, and was therefore at high risk of bias.

Other potential sources of bias

Owens 2014 was stopped early due to a change in hospital policy, at 74% of the enrolment target, leaving the study underpowered to demonstrate statistically significant differences, with unclear implications for the risk of other bias. The baseline characteristics of women assigned to the planned delivery and expectant monitoring groups appear to be similar in all studies, so there is low risk of other potential sources of bias for Broekhuijsen 2015, Hamed 2014, Koopmans 2009, and Majeed 2014.

Effects of interventions

See: **Summary of findings for the main comparison** Planned early delivery versus expectant management for hypertensive disorders from 34 weeks' gestation to term

Planned early delivery versus expectant management

See Summary of findings for the main comparison. We included five studies, involving 1819 women.

Primary outcomes

Two studies reported the**composite maternal outcome, including maternal mortality and severe morbidity** (Broekhuijsen 2015; Koopmans 2009). There was a lower risk of these severe adverse outcomes for women randomised to planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women, *evidence graded high*, Analysis 1.1). There were no clear differences between groups based on our subgroup analysis by gestational age, gestational week or condition (see Analysis 2.1; Analysis 3.1; Analysis 4.1).

The same two studies also reported the **composite perinatal outcome (including fetal or neonatal death and serious morbidity)**. There was not enough information to draw any conclusions about the effects on neonatal mortality and serious morbidity. Meta-analysis was not possible, due to substantial heterogeneity (I^2 = 87%, Tau^2 = 0.98) for this outcome between these two studies (1459 infants, Analysis 1.2). It is worth noting that Broekhuijsen 2015 found that infants in the planned early delivery group had a higher risk of respiratory distress syndrome than those in the expectant management group (RR 3.32, 95% CI 1.35 to 8.18, 703 infants, Analysis 2.2) with planned early delivery taking place at 34 to 37 weeks' gestation. However Koopmans 2009 showed

no evidence of differences in composite infant mortality and morbidity (RR 0.77, 95% CI 0.46 to 1.28, 756 infants, Analysis 2.3) with planned early delivery taking place later, at 36 to 41 weeks' gestation. There were no clear differences between groups based on our subgroup analysis by gestational age or gestational week (see Analysis 2.3; Analysis 3.2; Analysis 3.3). However Broekhuijsen 2015 have not yet published the composite outcomes by gestational age, so any possible adverse effects on infants born at the earliest gestations have not yet been explored.

Secondary outcomes

Maternal

There were no incidences of **maternal mortality** in the two studies that reported it (1457 women, Analysis 1.3). We found no clear differences between delivery and expectant management for the number of women experiencing **eclampsia** (RR 0.20, 95% CI 0.01 to 4.14, 1459 women, two studies, Analysis 1.4). There were no events reported for **pulmonary oedema** (703 women, one study, Analysis 1.5). Women who were assigned planned early delivery had a lower risk of **severe renal impairment** (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study, Analysis 1.6), and **HELLP syndrome** (RR 0.40, 95% CI 0.17 to 0.93, 1628 women, three studies, Analysis 1.7) than women assigned to expectant management. We found no clear differences between planned early delivery and expectant management for the number of women experiencing **thromboembolic disease** (RR 1.67, 95% CI 0.22 to 12.58, 1459 women, two studies, Analysis 1.8), **abruptio placentae** (RR 0.64, 95% CI 0.17 to 2.34, 1535 women, three studies, Analysis 1.9), or **postpartum haemorrhage** (RR 0.88, 95% CI 0.57 to 1.35, 741 women, one study, Analysis 1.10).

There was high heterogeneity between studies for women developing **severe hypertension** (I^2 = 79%, Tau^2 = 0.83). There was not enough information to draw any conclusions about the effects on severe hypertension (995 women, three studies, Analysis 1.11). Two studies (919 women) reporting this outcome found that planned early delivery was less likely to result in the progression to severe hypertension, while one study (74 women) found no difference. The study that found no difference had recruited pregnant women with chronic hypertension (Hamed 2014), while the women in the other two studies had mild pre-eclampsia (Owens 2014), gestational hypertension or mild pre-eclampsia (Koopmans 2009).

We found no clear differences between planned early delivery and expectant management for **caesarean section** (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, *evidence graded moderate,* Analysis 1.12), **assisted delivery (ventouse/forceps)** (RR 0.93, 95% CI 0.70 to 1.24, 1459 women, two studies, Analysis 1.13), or **endometritis (maternal morbidity of caesarean section)** (RR 0.75, 95% CI 0.17 to 3.35, 756 women, one study, Analysis 1.14). There were no events reported for **uterine rupture (maternal morbidity related to induction of labour)** (756 women, one study, Analysis 1.15). We found no clear differences between planned early delivery and expectant management for maternal **admission to a high care or intensive care unit** (RR 0.41, 95% CI 0.16 to 1.07, 708 women, one study, Analysis 1.16).

Women's experiences and views on the interventions were not reported in any of the included studies. However, Koopmans 2009 assessed women's health-related quality of life after planned early delivery or expectant management. They administered the Short-Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression Scale (HADS), and Symptom Checklist (SCL-90). Measurements were at baseline, six weeks postpartum and six months postpartum. They found no clear difference in these measures of health-related quality of life. (The numeric results are not presented in this review, because the outcomes do not correspond to those prespecified in the protocol. However, as these are important issues we have included this narrative summary of the results).

Several of the outcomes for this review were not reported by trial authors: **cerebrovascular event, liver haematoma or rupture, liver failure as defined above, dissemination intravascular coagulation,** and **antepartum haemorrhage.**

Fetal and neonatal

One study reported**fetal death**, with no events (756 infants, Analysis 1.17). There were very few events, and therefore not enough information to see if there was a difference in **neonatal death** (RR 2.00, 95% CI 0.19 to 21.14, 1535 infants, three studies, Analysis 1.18) and **grade III or IV intraventricular or intracerebral haemorrhage** (RR 6.92, 95% CI 0.36 to 133.41, 674 infants, one study, Analysis 1.19). We found no clear difference in the numbers of infants with **nectrotising enterocolitis** (RR 0.98, 95% CI 0.14 to 6.89, 1338 infants, two studies, Analysis 1.20). Babies allocated to planned early delivery had a higher risk of **acute respiratory distress syndrome or grade III/IV hyaline membrane disease** (RR 2.24, 95% CI 1.20 to 4.18, 1511 infants, three studies, Analysis 1.21). There was no clear difference between groups assigned to planned early delivery or expectant monitoring for **small-for-gestational age** as defined by trial authors (RR 1.58, 95% CI 0.89 to 2.79, 1001 infants, three studies, Analysis 1.22), **neonatal seizures** (RR 3.97, 95% CI 0.45 to 35.30, 699 infants, one study, Analysis 1.23), **Apgar score less than seven at five minutes** (RR 1.11, 95% CI 0.60 to 2.05, 1454 infants, two studies, Analysis 1.24), and **cord blood pH less than 7.1** or as defined by trial authors (RR 0.58, 95% CI 0.31 to 1.09, 1145 infants, two studies, Analysis 1.25). In the one study that reported **surfactant use**, no infants required it (639 infants, Analysis 1.26). Babies in the group allocated to planned early delivery were more likely to be **admitted to neonatal intensive care unit or high care unit** than those allocated to expectant management (RR 1.65,

95% CI 1.13 to 2.40, 1585 infants, four studies, Analysis 1.27). **Intubation and mechanical ventilation or continuous positive airway pressure support** was not reported in any of the included studies. There was a substantial difference in the incidence of **early neonatal sepsis** between the two studies that reported it, so results have not been pooled (1455 infants, two studies, Analysis 1.28).

Use of health-service resources

There was no clear difference in the **duration of hospital stay after delivery for mother** (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15; 925 women, two studies, *evidence graded moderate,* Analysis 1.29), and no clear difference in the **duration of hospital stay after delivery for baby** (MD -0.20 days, 95% CI -0.57 to 0.17, 756 infants, one study, *evidence graded moderate,* Analysis 1.30).

Economic outcomes

The **costs to health service resources: short-term and long-term for both mother and baby** and **costs to the woman, her family, and society** were not reported in the included studies.

DISCUSSION

Summary of main results

We included five studies involving 1819 women, comparing planned early delivery versus expectant management for hypertensive disorders from 34 weeks to term.

Fewer women who had hypertensive disorders of pregnancy experienced severe adverse outcomes (composite maternal mortality and severe morbidity) when they were allocated to planned early delivery. Planned early delivery was also associated with lower levels of HELLP syndrome and severe renal impairment. There was no clear difference in any of the other maternal outcomes reported by the included studies.

There was not enough information to draw any conclusions about the effects on neonatal mortality and severe morbidity, as there were limited data assessing all hypertensive disorders as one group. Planned early delivery was associated with higher levels of respiratory distress syndrome, and NICU admission. There was no clear difference for other infant outcomes reported by the included studies.

No difference was shown between planned early delivery and expectant management in the proportion of women needing a caesarean section, and in the duration of hospital stay after delivery for mother or baby.

(See Summary of findings for the main comparison.)

Overall completeness and applicability of evidence

The studies included in this review addressed the objective, which was to determine the risks and benefits of expectant management versus planned early delivery for the hypertensive disorders of pregnancy after 34 weeks gestation. The management of pre-eclampsia diagnosed before 34 weeks is described in another Cochrane Review (Churchill 2013). The majority of women included in this review had mild pre-eclampsia and gestational hypertension, with fewer women having chronic hypertension. Most of the women included came from the Netherlands, with smaller numbers from India, USA and Saudi Arabia, making the review globally applicable. The results are applicable to general obstetric practice when the hypertensive disorders of pregnancy are considered together, but an individual patient meta-analysis may provide more answers as it would allow for more statistical power when reviewing the different types of hypertensive disorders in pregnancy.

Quality of the evidence

Two fairly large, well-designed trials contributed the majority of the evidence to this review (Broekhuijsen 2015; Koopmans 2009). Due to the nature of the intervention, no studies attempted to blind participants or clinicians to group allocation. We did not downgrade studies for this; however, women and staff would have been aware of the intervention and this may have affected aspects of care and decision-making, for example, whether to carry out a caesarean section.

We graded the level of evidence as high (composite maternal mortality and morbidity), moderate (caesarean section, duration of hospital stay after delivery for mother, and duration of hospital stay after delivery for baby), or low (composite infant mortality and morbidity) (see Summary of findings for the main comparison). Where the evidence was downgraded, it was mostly because the CIs were wide, crossing both the line of no effect and appreciable benefit or harm.

Potential biases in the review process

The assessment of risk of bias involves subjective judgements. This potential limitation is minimised by following the procedures in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with review authors independently assessing studies and resolving any disagreement through discussion, and if required involving a third assessor in the decision.

Agreements and disagreements with other studies or reviews

The findings of this review show that planned early delivery for hypertensive disorders of pregnancy are associated with less severe maternal adverse outcomes. This analysis looks at all the hypertensive diseases, namely chronic hypertension, gestational hypertension and mild pre-eclampsia as one group. The National Institute for Health and Clinical Excellence guidelines on hypertension in pregnancy: diagnosis and management (NICE 2010), the American College of Obstetricians and the Society for Maternal-Fetal Medicine and Gynecologists Committee opinion number 560 on medically indicated late-preterm and early term deliveries (ACOG No. 560 2013) and the Society of Obstetric Medicine of Australia and New Zealand guideline for the management of hypertensive disorders of pregnancy (Lowe 2014) set different gestational ages for delivery based on the hypertensive condition.

AUTHORS' CONCLUSIONS

Implications for practice

For hypertensive disorders as a group, based on the limited data available for this review, planned early delivery appears to be better for the mother after 34 weeks' gestation. However, it is unclear whether planned early delivery increases risks for the baby, especially at earlier gestations, and more data are needed to guide practice. It is also unclear whether planned early delivery is advisable for different hypertensive conditions. Further studies are needed to look at the individual conditions before this is implemented into clinical practice.

Implications for research

Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions. These studies should include the maternal outcomes of mortality and severe morbidity like eclampsia, a cerebral vascular event, pulmonary oedema, severe renal impairment, a liver haematoma or rupture, liver failure, HELLP syndrome, DIC, thromboembolic disease and abruptio placentae. Perinatal outcomes that should be included are fetal or neonatal death, grade III or IV intraventricular or intracerebral haemorrhage, NEC, ARDS or grade III/IV hyaline membrane disease, small-for-gestational age and neonatal seizures. The outcomes of the incidence of caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby should also be included.

An individual patient meta-analysis on the data currently available would provide further information on the outcomes of the different types of hypertensive disease encountered in pregnancy.

ACKNOWLEDGEMENTS

Denise Atherton for administrative assistance; Lynn Hampson for the literature search.

CC's contribution to this project was supported by the Discovery Foundation and the South African Medical Association.

HW's contribution to this project was supported by the National Institute for Health Research, via Cochrane Programme Grant funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

The Cochrane generic protocol on Interventions for preventing pre-eclampsia and its consequences (Meher 2005) was used in preparation of the protocol for this review.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

This project was supported by the National Institute for Health research, via Cochrane Infrastructure and Cochrane Programme Grant funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Broekhuijsen 2015 *{published data only}*

Broekhuijsen K, Langenveld J, Van Baaren G, Van Pampus MG, Van Kaam AH, Groen H, et al. Correction: Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial. *BMC Pregnancy and Childbirth* 2013;**13**:232.

* Broekhuijsen K, Van Baaren GJ, Van Pampus M, Ganzevoort W, Sikkema M, Woiski M, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015;**385**:2492–501.

Broekhuijsen K, Van Baaren GJ, Van Pampus M, Sikkema M, Woiski M, Oudijk M, et al. Delivery versus expectant

monitoring for late preterm hypertensive disorders of pregnancy (HYPITAT-II): a multicenter, open label, randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2014;**210**(1 Suppl):S2.

Langenveld J, Broekhuijsen K, Van Baaren GJ, Van Pampus MG, Van Kaam AH, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): A multicentre, open-label randomised controlled trial. *BMC Pregnancy and Childbirth* 2011;**11**: 50.

Hamed 2014 *{published data only}*

Hamed HO, Alsheeha MA, Abu-Elhasan AM, Elmoniem AEA, Kamal MM. Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery. *International Journal of Gynecology and Obstetrics* 2014;**17**: 15–20.

Koopmans 2009 *{published data only}*

Bijlenga D, Birnie E, Mol B, Bekedam D, De Boer K, Drogtop A, et al. Health-related quality of life after induction of labor or expectant management in pregnancy-induced hypertension and pre-eclampsia at term. *Hypertension in Pregnancy* 2008;**27**(4):518.

Bijlenga D, Koopmans CM, Birnie E, Mol BWJ, Van der Post JA, Bloemenkamp KW, et al. Health-related quality of life after induction of labor versus expectant monitoring in gestational hypertension or preeclampsia at term. *Hypertension in Pregnancy* 2011;**30**(3):260–74.

Hermes W, Koopmans CM, Van Pampus MG, Franx A, Bloemenkamp KW, Van der Post J, et al. Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: do women's postpartum cardiovascular risk factors differ between the two strategies?. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2013;**171**(1):30–4.

Koopmans C, Ven den Berg P, Moll BW, Groen H, Willekes, Kwee A, et al. Pregnancy-induced hypertension and preeclampsia after 36 weeks: induction of labour versus expectant monitoring. The HYPITAT trial. *Hypertension in Pregnancy* 2008;**27**(4):421.

Koopmans CM, Bijlenga D, Aarnoudse JG, Van Beek E, Bekedam DJ, Van den Berg PP, et al. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial. *BMC Pregnancy and Childbirth* 2007;**7**:14.

* Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009;**374**(9694):979–88.

Tajik P, Van der Tuuk K, Koopmans C, Groen H, Van Pampus M, Van der Berg P, et al. Should cervical ripeness play a role in the decision for labor induction in women with gestational hypertension or mild preeclampsia at term: an exploratory analysis of the HYPITAT trial. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1): S349.

Tajik P, Van der Tuuk K, Koopmans CM, Groen H, Van Pampus MG, Van der Berg PP, et al. Should cervical favourability play a role in the decision for labour induction in gestational hypertension or mild pre-eclampsia at term? An exploratory analysis of the HYPITAT trial. *BJOG: an international journal of obstetrics and gynaecology* 2012;**119** (9):1123–30.

Van Der Tuuk K, Koopmans C, Aarnoudse J, Rijnders R, Van Beek J, Porath M, et al. Prediction of deterioration of the clinical condition in women with preeclampsia or pregnancy induced hypertension at term. *Hypertension in Pregnancy* 2008;**27**(4):464.

Van Pampus M. Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labour versus expectant monitoring. A comparison of maternal and neonatal outcome, maternal quality of life and costs. Netherlands Trial Register (www.trialregister.nl) (accessed 1 November 2005).

Vijgen S, Koopmans C, Opmeer B, Groen H, Bijlenga D, Aarnoudse J, et al. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). *BJOG: an international journal of obstetrics and gynaecology* 2010;**117**:1577–85.

Vijgen S, Opmeer B, Mol BW, Bijlenga D, Burggraaff J, Van Loon A, et al. An economic analysis of induction of labor and expectant management in women with pregnancy-induced hypertension or preeclampsia at term (HYPITAT Trial). *Hypertension in Pregnancy* 2008;**27**(4):519.

Visser S, Hermes W, Koopmans C, Van Pampus MG, Franx A, Mol BW, et al. Hypertension 6 weeks and 21/2 years after term pregnancies complicated by hypertensive disorders. *Reproductive Sciences* 2011;**18**(3 Suppl 1):354A.

Majeed 2014 *{published data only}*

Majeed A, Kundu S, Singh P. Study on induction of labour versus expectant management in gestational hypertension or mild preeclampsia after 36 weeks of gestation. *BJOG: an International Journal of Obstetrics and Gynaecology* 2014;**121** (Suppl 2):118.

Owens 2014 *{published data only}*

Martin JN, Owens MY, Thigpen B, Parrish MR, Keiser SD, Wallace K. Management of late preterm pregnancy complicated by mild preeclampsia: A prospective randomized trial. *Pregnancy Hypertension* 2012;**2**(3):180.

NCT00789919. Mild preeclampsia near term: deliver or deliberate?. clinicaltrials.gov/ct2/show/NCT00789919 Date first received: 12 November 2008.

* Owens MY, Thigpen B, Parrish MR, Keiser SD, Sawardecker S, Wallace K, et al. Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks?. *Journal of the Mississippi State Medical Association* 2014;**55**(7): 208–11.

References to studies excluded from this review

Ramrakhyani 2001 *{published data only}*
Ramrakhyani N, Sharma SK, Sankhla J, Sharma SK. Role of active management of pregnancy with hypertension in improving maternal and foetal outcome. *Journal of the Association of Physicians of India* 2001;**49**(1):Abstract no: 149.

Tukur 2007 *{published data only}*
Tukur J, Umar NI, Khan N, Musa D. Comparison of emergency caesarean section to misoprostol induction for the delivery of antepartum eclamptic patients: a pilot study. *Nigerian Journal of Medicine* 2007;**16**(4):364–7.

References to ongoing studies

Shennan 2013 *{published data only}*
ISRCTN01879376. PHOENIX - Pre-eclampsia in HOspital: Early iNductIon or eXpectant management. isrctn.com/ISRCTN01879376 Date first received: 20 November 2013.

Additional references

Abalos 2013
Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2013;**170**(1):1–7. [doi: 10.1016/j.ejogrb.2013.05.005]

ACOG Hypertension in Pregnancy 2013
Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstetrics and Gynecology* 2013;**122**(5):1122–31.

ACOG No. 560 2013
Committee Opinion No. 560. American College of Obstetricians and Gynaecologists. Medically indicated late-preterm and early-term deliveries. Obstetrics and Gynecology 2013; Vol. 121, issue 4:908–10.

August 2012
August P, Sibai BM. Preeclampsia: Clinical features and diagnosis. www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis (accessed 10 March 2014).

Barton 2001
Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *American Journal of Obstetrics and Gynecology* 2001;**184**(5):979–83.

Belizan 1980
Belizan JM, Villar J. The relationship between calcium intake and edema, proteinuria, and hypertension-gestosis: an hypothesis. *American Journal of Clinical Nutrition* 1980; **33**(10):2202–10.

Boyle 2012
Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes art 3 and 5 years: population based cohort study. *BMJ* 2012;**344**:e896. [DOI: 10.1136/bmj.e896

Bujold 2014
Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. *Prenatal Diagnosis* 2014;**34**(7):642–8.

Churchill 2013
Churchill D, Duley L, Thornton JG, Jones L. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD003106.pub2

Davis 2007
Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L, et al. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. *Hypertension in Pregnancy* 2007;**26**(1):77–87.

De Regil 2011
De Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008873.pub2

Dietz 2012
Dietz PM, Rizzo JH, England LJ, Callaghan WM, Vesco KK, Bruce FC, et al. Early term delivery and health care utilization in the first year of life. *Journal of Pediatrics* 2012; **161**(2):234–9.

Dolea 2003
Dolea C, AbouZahr C. Global burden of hypertensive disorders of pregnancy in the year 2000. Evidence and Information for Policy (EIP), World Health Organization, Geneva, July 2003. www.who.int/healthinfo/statistics/bod_hypertensivedisordersofpregnancy.pdf (Accessed on December 12, 2012).

Duley 2009
Duley L, Henderson-Smart DJ, Walker GJA. Interventions for treating pre-eclampsia and its consequences: generic protocol. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD007756

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hofmeyr 2014
Hofmyer GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD001059.pub4

Hutcheon 2011
Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of

pregnancy. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2011;**25**(4):391–403.

Khan 2006
Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: systematic review. *Lancet* 2006;**367**(9516):1066–74.

Lowe 2014
Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. Guideline for the Management of Hypertensive Disorders of Pregnancy. Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) 2014.

Magee 2008
Magee LA, Helewa M, Moutquin JM, Von Dadelszen P, Hypertension Guideline Committee, Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRHS) Scholars. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Journal of Obstetrics and Gynaecology Canada: JOGC* 2008; **30**(3 Suppl):S1.

Magee 2014
Magee LA, Pels A, Helewa M, Rey E, Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health* 2014; 4(2):105–45.

Magloire 2012
Magloire L, Funai EF. Gestational hypertension. www.uptodate.com/contents/gestational-hypertension (accessed 10 March 2014).

Maslow 2000
Maslow AS, Sweeny AL. Elective induction of labor as a risk factor for cesarean delivery among low-risk women at term. *Obstetrics and Gynecology* 2000;**95**(6 Pt 1):917–22.

Meher 2005
Meher S, Duley L, Prevention of Pre-eclampsia Cochrane Review Authors. Interventions for preventing pre-eclampsia and its consequences: generic protocol. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/ 14651858.CD005301

NICE 2010
National Collaborating Centre for Women's and Children's Health. *Hypertension in Pregnancy: the Management of Hypertensive Disorders During Pregnancy. NICE Clinical Guideline 107*. London: National Institute for Health and Clinical Excellence, August 2010.

Norwitz 2013
Norwitz ER, Funai EF. Expectant management of severe preeclampsia. www.uptodate.com/contents/expectant-management-of-severe-preeclampsia (accessed 10 March 2014).

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Saftlas 1990
Saftlas AF, Olson DR, Franks AL, Atrash AK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. *American Journal of Obstetrics and Gynecology* 1990;**163**(2):460–5.

Sibai 2005
Sibai B, Dekker G, Kupferminc G. Pre-eclampsia. *Lancet* 2005;**365**(9461):785–99.

Spong 2011
Spong CY, Mercer BM, D'alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstetrics and Gynecology* 2011;**118**(2 Pt 1):323–33.

Steegers 2010
Steegers EAP, Van Dadelszen P, Pijnenbong R. Pre-eclampsia. *Lancet* 2010;**376**:631–44.

Tita 2009
Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *New England Journal of Medicine* 2009;**360**(2):111–20.

Villar 2003
Villar J, Say L, Gülmezoglu M, et al. Eclampsia and preeclampsia: a worldwide health problem for 2000 years. In: Critchley H, Maclean A, Poston L, Walker J editor (s). *Pre-eclampsia*. London, England: RCOG Press, 2003: 57–72.

Wang 2004
Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. *Pediatrics* 2004;**114**(2): 372–6.

WHO 2011
World Health Organization. *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*. Geneva: WHO, 2011.

Wilmink 2010
Wilmink FA, Hukkelhoven CW, Lunshof S, Mol BW, Van der Post JA, Papatsonis DN. Neonatal outcome following elective cesarean section beyond 37 weeks of gestation: a 7-year retrospective analysis of a national registry. *American Journal of Obstetrics and Gynecology* 2010;**202**(3):1–8.

References to other published versions of this review

Novikova 2011
Novikova N, Cluver C, Koopmans CM. Delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2011, Issue 8. [DOI: 10.1002/ 14651858.CD009273

* *Indicates the major publication for the study*

CHAPTER 5: Conclusion and future directions

5.1 Conclusion

Preeclampsia remains one of the most common causes of maternal and perinatal morbidity and mortality.[1,2] Making inroads into the global disease burden of preeclampsia is therefore an important imperative if we are to realize the goals set by the World Health Organisation to reduce the global maternal mortality ratio (MMR) to fewer than 70 maternal deaths per 100,000 live births by 2030.[63] Much attention has been directed to screening for early preterm preeclampsia in early pregnancy, yet this is only a small part of the solution since screening modalities will not be able to identify all who are at risk of preeclampsia and preventative treatments, like aspirin, will not prevent all cases.[64–66] Importantly, the global burden of preeclampsia occurs mostly in low resource settings, where screening and prevention is simply not feasible. This highlights the continuing need for an effective therapeutic for preterm preeclampsia that may delay or arrest disease progression.

To have global impact, any treatment for preeclampsia ideally should be suited for low-and-middle income countries, ie. be cheap, off patent, widely accessible, well tolerated, have an established safety profile in pregnancy and not require prolonged refrigeration. A therapeutic target should ideally reduce placental production and release of antiangiogenic factors and improve maternal vascular function. Preclinical data suggested that proton pump inhibitors, specifically esomeprazole, met all these criteria. To translate these laboratory findings into the clinic, we performed a double-blind randomised controlled trial of 40 mg of daily esomeprazole versus placebo in which we not only obtained data on clinical outcomes, but we also derived important insights from integrating biomarker studies and

pharmacokinetics. Esomeprazole did not prolong gestation among women with early preterm preeclampsia in this trial, and there were no significant differences in maternal and perinatal outcomes by treatment group. Circulating levels of sFlt1 and other antiangiogenic markers were extremely high among the cohort and were not lowered by esomeprazole. The drug appeared safe and was well tolerated. In pharmacokinetic studies, we found that esomeprazole was present in the maternal circulation, but concentrations were relatively low compared with those required to elicit tissue/cell responses in our previous laboratory studies. This raises the possibility that higher doses, more frequent dosing or intravenous preparations may be necessary to see beneficial effects. Levels of esomeprazole in the umbilical cord blood were very low, or not detectable, which provides further reassurance that very little reaches the fetal compartment.

Despite this negative finding, we have demonstrated our capacity to perform high quality therapeutic trials in settings where such interventions are needed most. Our trial was run at a single center, which allowed us to attain a high recruitment rate, closely monitor compliance, and collect uniform high-quality data including biospecimens. We undertook parallel assessment of preeclampsia biomarkers and drug pharmacokinetics, which have helped identify potential reasons why the treatment may not have worked but have also been helpful to inform the design of future interventional trials. Importantly, by embedding this trial in an academic centre that serves a population with a high incidence of early preterm preeclampsia, we overcame the problem faced by previous trials of low recruitment. We propose this may be an optimal approach when designing clinical trials for early preterm preeclampsia.

Our future work proposes ongoing therapeutic trials of agents that may have efficacy to prevent, or treat, preeclampsia. With a focus on clinical translation, these drugs must first have a well-established safety profile in pregnancy, be cheap, accessible and well tolerated. Our laboratory pipeline has enabled us to undertake the necessary *in vitro* and *in vivo* studies to identify which of these agents have the most promise; i.e.. reduce placental production and release of antiangiogenic factors, and reduce maternal endothelial dysfunction, both key pathological events in preeclampsia. Through this program, we have identified new drug candidates. The research undertaken by the PhD has now set up a clinical trials infrastructure, which we plan to use to run a succession of clinical trials. The second interventional trial for treatment of early preterm preeclampsia with metformin is already well underway.

We have shown that the presence of coexisting fetal growth restriction at the time of diagnosis is an important determinant of outcome in early preterm preeclampsia being managed expectantly. These pregnancies have a significantly shorter latency. Delivery is most likely to be triggered by a fetal indication and will almost universally end in caesarean section. The presence of coexisting FGR is associated with increased risks of neonatal mortality and serious morbidity. This high-quality prospective data usefully informs clinical counselling and decision making in women with early preterm preeclampsia. It is relevant to future therapeutic trials, where the fetal trigger for delivery may persist even if an effective intervention is identified that may slow maternal disease progression.

Late preterm preeclampsia is associated with significant maternal morbidity. The available evidence favours delivery on maternal grounds, but limitations of existing data make it difficult to reliably ascertain the relative fetal benefit and risk. More research is needed with particular emphasis on stratification by

different disease sub-type and gestational age epochs. This would help with clinical decision making as well as the design of future interventional trials. If our future work identifies a safe and effective therapeutic for preeclampsia, these studies would determine whether expectant management and treatment could confer perinatal benefit without compromising maternal outcomes, even in late preterm preeclampsia.

5.2 Future directions

This research has created the momentum and infrastructure required to build research capacity and leadership in preeclampsia at Tygerberg Hospital, Stellenbosch University, South Africa. Our next steps include the testing of new therapeutics for preterm preeclampsia. We propose to test the most promising therapeutic candidates identified in the laboratory into clinical care, through testing them in appropriately powered randomised placebo-controlled trials (RCT). In the last 6 months we have commenced an interventional trial of metformin, and recruitment is already one third complete (n=56 out of a planned recruitment total of 150, as of October 2018). The protocol has been submitted for publication. Importantly, our intervention has been appropriately informed by a preceding pharmacokinetics study of 15 participants with preterm preeclampsia which shows a drug exposure profile that appears more promising than that seen with 40 mg of esomeprazole.

Our vision is to continue running clinical trials of novel agents for the treatment of early preterm preeclampsia with embedded pharmacokinetics and mechanistic insights with clinical endpoints.

APPENDICES

1. PIE trial protocol

The Pre-eclampsia Intervention with Esomeprazole (PIE) trial: a double blind randomised, placebo-controlled trial to treat early onset pre-eclampsia

Phase II study

CLINICAL TRIAL PROTOCOL

Full title of trial	The Pre-eclampsia Intervention with Esomeprazole (PIE) trial: a double blind randomised, placebo-controlled trial to treat early onset pre-eclampsia.
Short title	PIE trial
Version and date	22 August, 2014 Version 2.4
Ethics approval	Protocol number M14/09/038 Federal Wide Assurance Number 00001372 Institutional Review Board (IRB) Number: IRB0005239
NHREC Application ID	3649
Trial medication	Esomeprazole
Phase of trial	Phase II
Principal investigator	Dr Catherine Anne Cluver
Supervisors/ Co-investigators	Professor Stephen Tong (external) Professor Susan Walker (external) Prof Gerhardus Theron (internal) Prof Ben Mol Prof DR Hall Dr N Hannan Dr H Hiscock

CONTACT DETAILS

Principal Investigator for clinical trial
Dr Catherine Cluver
Tygerberg Hospital
University of Stellenbosch
Address: 11 Bath Street, Gardens, Cape Town, South Africa 8001
Tel: +27823210298
Fax: +27219322455
Email: cathycluver@hotmail.com

External Supervisors/ Co-Investigators/ Promoters
Prof Stephen Tong
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: stong@unimelb.edu.au

Prof Susan Walker
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: spwalker@unimelb.edu.au

Internal Supervisor/ Co-Investigator/ Co-promoter
Prof Gerhadus Theron
Tygerberg Hospital
University of Stellenbosch
Tel: +27 21 938 9209
Email: gbth@sun.ac.za

Prof Ben Mol
The Robinson Institute, School of Paediatrics and Reproductive Health
University of Adelaide
Phone: +61 434122170
Email: ben.mol@adelaide.edu.au

Prof David Hall
University of Stellenbosch
Email: drh@sun.ac.za

Principal investigators for Laboratory Studies

Prof Stephen Tong
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: stong@unimelb.edu.au

Dr Natalie Hannan
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: nhannan@unimelb.edu.au

Trial Design and Statistics

Dr Richard Hiscock
Mercy Hospital for Women
Email: richardjhiscock@gmail.com

Laboratory Coordination

South Africa:

Dr Catherine Cluver
Tygerberg Hospital
University of Stellenbosch
Tel: +27823210298
Email: cathycluver@hotmail.com

Australia:

Prof Stephen Tong
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: stong@unimelb.edu.au

TRIAL COMMITTEES

Trial Steering Committee

Chair:

Prof Ben Mol
Professor of Obstetrics and Gynaecology
The Robinson Institute, School of Paediatrics and Reproductive Health
University of Adelaide
Phone: +61 434122170
Email: ben.mol@adelaide.edu.au

Members:

Dr Catherine Cluver
Tygerberg Hospital
University of Stellenbosch
Tel: +27823210298
Email: cathycluver@hotmail.com

Prof Stephen Tong
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: stong@unimelb.edu.au

Prof Susan Walker
Mercy Hospital for Women
University of Melbourne
Tel: +613 8458 4380
Email: spwalker@unimelb.edu.au

Data Monitoring Committee

Chair:

Dr Jim Holberton
Consultant Paediatrician

Mercy Hospital for Women
Email: JHolberton@mercy.com.au
Tel: +61 3845 84723
Fax: +61 3945 95389

Members:

Dr Jonathan Morris
Professor Obstetrics and Gynaecology
Kolling Institute of Medical Research
University of Sydney
Tel +61 2 9926 4500
Email: jonathan.morris@sydney.edu.au
Website: http://sydney.edu.au/medicine/northern

Statistician: Dr Lisa Yelland
NHMRC Postdoctoral Research Fellow
Women's & Children's Health Research Institute and School of Population Health
The University of Adelaide
Email: lisa.yelland@adelaide.edu.au
Phone: 8313 3215 / 8313 1428
Fax: 8223 4075
Website: http://www.adelaide.edu.au/directory/lisa.yelland

Protocol Versions

2.4

Signatures

The investigators have discussed this protocol. The investigators agree to perform this trial as set out by the protocol and will only deviate from the protocol in the case of a medical emergency or when the departure is mutually agreed upon in writing by all parties involved.

Principal investigator: 

Date: August 2014

Abbreviations

CTG	Cardiotocograph
FDA	Food and Drug Administration
GA	Gestational age
HO-1	Heme oxygenase-1
ITT	Intention to treat
ISSHP	International Society for the Study of Hyperensive disorders in Pregnancy
KEAP-1	Kelch-like ECH-associated protein 1
mg	Milligrams
Nrf-2	Nuclear factor (erythroid-derived 2)-like 2
PIE	Pre-eclampsia Intervention with Esomeprazole
PPIs	Proton pump inhibitors
PRES	Posterior reversible encephalopathy syndrome
sEng	Soluble Endoglin
sFlt1	Soluble Fms Like Tyrosine Kinase -1
STAMP	STatins to AMeliorate early onset Pre-eclampsia
TNF	Tumour Necrosis Factor
TR	Treatment received
VCAM-1	Vascular Cell Adhesion Molecule -1

CONTENTS

1. Summary/ Synopsis

Title

The Pre-eclampsia Intervention with Esomeprazole (PIE) trial: a double blind randomised, placebo-controlled trial to treat early onset pre-eclampsia.

Short Introduction and literature overview

Pre-eclampsia is globally responsible for 60,000 maternal deaths per year, and far greater numbers of fetal losses. It is one of the leading causes of maternal mortality in South Africa and a major problem in developing countries. At present there is no treatment for pre-eclampsia apart from delivery which results in severe perinatal morbidity and mortality associated with prematurity. This is especially a problem in developing countries where there is a shortage of neonatal intensive care and high care beds.

Esomeprazole is a proton pump inhibitor widely used for the treatment of gastric acid-related disorders, such as peptic ulcer disease and gastro-oesophageal reflux. Recently preclinical data has been generated showing that the proton pump inhibitor esomeprazole has potent biological effects making it a lead candidate to treat early onset pre-eclampsia.

Esomeprazole:

1) ***decreases the release of soluble endoglin (sEng) and soluble Fms-like Tyrosine Kinase 1 (sFlt-1)*** from both primary placental tissue and primary endothelial cells in vitro. These are anti-angiogenic factors released from the placenta that are thought to play a central role in the pathogenesis of pre-eclampsia.
2) ***upregulates heme oxygenase-1***, a potent 'cytoprotective' molecule in the placenta.
3) **decreases endothelial dysfunction** in in vitro assays.

Esomeprazole is inexpensive and is available in most developing countries. If proven to work it could have a major impact on maternal and perinatal health in developing countries.

Research question

Can a single daily dose of esomeprazole, compared with placebo, prolong gestation for a further 5 days and improve biochemical markers in women with early onset pre-eclampsia managed with expectant management.

Aims:

Primary aim

- To examine whether 40 mg of daily esomeprazole can safely further prolong gestation for 5 days in women with early onset pre-eclampsia diagnosed 26+0 – 31+6 weeks, compared to expectant management alone.

Secondary aims

- To determine whether a single daily dose of 40 mg esomeprazole improves 1) maternal, 2) fetal and 3) neonatal outcomes in early onset pre-eclampsia compared to placebo.
- To examine whether a single daily dose of 40 mg esomeprazole can significantly decrease circulating levels of sFlt-1 and/ or sEng in women with early onset pre-eclampsia, compared to placebo.
- To examine whether a single daily dose of 40 mg esomeprazole is safe and well tolerated in the mother, fetus and neonate compared with placebo.

Methods (Overview)

We will perform a double blind randomised controlled trial of 120 women with early onset pre-eclampsia. Informed consent will be obtained. Pregnant women between the ages of 18 and 50 years who present with early onset pre-eclampsia at a gestation of 26+0 to 31+6 weeks at Tygerberg Hospital who are considered stable enough to undergo expectant management will be randomised to either esomeprazole or placebo. They will receive either 40mg of daily esomeprazole or an identical placebo daily. The ongoing management and decision to deliver will be left to the discretion of the treating clinician who will be blinded to treatment group allocation. We will obtain clinical information, including maternal, fetal and neonatal outcomes, clinical investigation results of mother, fetus and neonate, and data on tolerability and safety. Blood samples and urine samples will be collected at enrolment and then twice weekly when routine blood are taken. At delivery we will collect a cord blood sample and placental tissue if consent has been given.

Timeline

4 years (2014 to 2017)

Ethical considerations

Pregnant women are a vulnerable population but early onset pre-eclampsia is a major cause of maternal, fetal and neonatal morbidity and mortality. Esomeprazole has been widely used in pregnancy and may be a treatment for this serious condition. For this reason we believe that it is important to conduct this trial.

Anticipated overall outcome

By the end of this phase II study, we will obtain evidence whether esomeprazole may be able to allow women diagnosed with early onset pre-eclampsia to safely gain gestation and whether it is a possible treatment option.

2.0 Background

2.1 Introduction

Pre-eclampsia is a major disease of pregnancy

Pre-eclampsia is one of the most serious complications of pregnancy affecting 3-8 % of pregnancies worldwide [1,2]. It is a multi-system disorder involving maternal vessels (causing hypertension and endothelial dysfunction), the kidneys, the liver, the lungs, the haematological system, the cardiovascular system and the fetoplacental unit[3]. In its most severe form, it affects the brain, causing seizures (eclampsia), cerebrovascular events and even death.

It is a leading cause of maternal and fetal/neonatal morbidity[4]. Globally, pre-eclampsia is responsible for >60,000 maternal deaths annually[5] and in South Africa hypertensive disorders of pregnancy are responsible for 14% of maternal deaths[6]. In the United States it is estimated that for every pre-eclampsia related death there are probably 50-100 other women who experience significant morbidity associated with pre-eclampsia[7].

There is no known treatment for pre-eclampsia apart from delivery

Despite considerable research the only treatment available is termination/delivery of the pregnancy[8]. This poses a difficult clinical dilemma for early onset pre-eclampsia. Clinicians are often forced to deliver early on maternal indications to prevent major maternal morbidity (ie severe maternal organ injury), as there are no treatments to arrest disease progression, but in doing so, inflict severe prematurity on the fetus. In particular, fetuses delivered at less than 33 weeks' gestation are at significant risk of severe disability including cerebral palsy, stroke (intracerebral bleeding), retinopathy of prematurity, chronic lung disease and death[9,10].

Currently, there are trials investigating the possible use of pravastatin to treat pre-eclampsia (STAMP trial, UK based study), and to prevent it (Pravastatin for the Prevention of Pre-eclampsia, run by the MFM network, a US based study). There are no other significant trials of orally available small molecules to treat pre-eclampsia that we are aware of.

Why is it important to find a treatment for pre-eclampsia?

If an affordable and safe treatment was available it could temporise the disease progression of pre-eclampsia thereby delaying delivery to gain gestation. This could save the lives of many infants and decrease the hospital burden caused by iatrogenic prematurity and is in keeping with the United Nations Development goals to reduce child mortality and improve maternal health.

2.2 Pathogenesis of Pre-eclampsia

Oxidative stress, anti-angiogenic factors and endothelial dysfunction: key steps in the pathogenesis of pre-eclampsia

In normal pregnancy, the placenta implants and invades into the inner third of the myometrium. It remodels the maternal spiral arterioles, stripping them of the contractile smooth muscle and turning them into large non-contractile vessels. The maternal vascular system becomes a high capacitance (i.e. high volume) and low pressure system. This remodelling optimises the amount of maternal blood flow to the placental interface, maximising oxygen and nutrient exchange.

In early pregnancy, the pre-eclamptic placenta fails to correctly implant in the myometrium. There is shallow placental implantation leading to inadequate remodelling of the spiral arterioles. The maternal arterioles become a low capacitance and high pressure system. As a consequence, there is less exchange of oxygen and nutrients and the placenta is rendered chronically hypoxic for the remainder of the pregnancy. Chronic placental hypoxia may induce generalised vasoconstriction in the fetoplacental circulation with increased resistance to umbilical artery blood flow. In addition, the shallow implantation also results in chronic oxidative stress in the placenta[11].

There are other schools of thought that believe the primary insult during the first stage is predominantly oxidative stress and ischaemic/re-perfusion injury rather than hypoxia[12]. Whatever the mechanism of injury, most agree shallow placental implantation is an intrinsic key step to this first stage.

In the second half of the pre-eclamptic pregnancy the persistent oxidative stress and hypoxia provokes the release of soluble Fms Like Tyrosine Kinase -1 (sFlt1)[13] and soluble endoglin (sEng)[14] into the maternal circulation. These are anti-angiogenic factors, released in vastly

elevated amounts in pre-eclampsia[13], which cause maternal endothelial dysfunction[8] (injury to maternal vessels) and the end-organ injury seen with clinical disease[3].

Thus, key aspects in the pathophysiology of pre-eclampsia are 1) placental oxidative stress (and hypoxia) 2) placental release of the anti-angiogenic factors sFlt1 and soluble endoglin and 3) maternal endothelial dysfunction. A drug that can counter these pathological steps could be a strategy to treat pre-eclampsia.

The greatest benefit for a potential therapeutic to treat pre-eclampsia would be one that could be administered to pregnancies diagnosed with early onset pre-eclampsia before 32-33 weeks. It is possible that such a therapeutic could significantly quench the disease process and stabilise the maternal condition. If so, it could allow the pregnancy to safely continue to a gestation where the risks to the fetus are much diminished (e.g. >34 weeks gestation). This could diminish the morbidity rates of many neonates, particularly in developing countries where babies of less than 34 weeks gestation are very vulnerable.

2.3 Biological role of proton pump inhibitors as possible therapy

The proton pump inhibitor esomeprazole: an unexpected drug candidate for pre-eclampsia.

The Translational Obstetrics Group at Melbourne University has generated strong preclinical evidence suggesting esomeprazole may have potent actions giving it significant potential as a treatment for pre-eclampsia (unpublished data).

Esomeprazole counters three key steps in pre-eclampsia pathogenesis, by:

1) **Up-regulating heme oxygenase-1 (HO-1),** a key cytoprotective enzyme with potent **anti-oxidant** actions in cells.

2) **Strongly decreasing the release of antiangiogenic factors sFlt-1 and sEng.**

3) Quenching **endothelial dysfunction.**

2.3.1 Proton pump inhibitors up regulate a key placental protective enzyme: heme-oxygenase-1

Seminal work during the 1970-80s revealed oxidative stress (present both in placenta and maternal vessels) is a key ingredient in the pathogenesis of pre-eclampsia[15]. Heme-oxygenase-1 (HO-1) is a key cellular protection enzyme. It mobilises a number of anti-oxidant defenses and switches on cytoprotective genes[16]. It has been proposed that decreased HO-1 is important in the pathogenesis of pre-eclampsia and leads to increased oxidative stress seen in the disease[17-20]. Many researchers have thus speculated that identifying a drug that up-regulates HO-1 could be an effective strategy to treat pre-eclampsia[21]. HO-1 has therefore emerged as a key molecule of interest in the field.

The Translational Obstetrics Group has found that proton pump inhibitors (PPIs) potently upregulate HO-1 expression (ie a class effect common to all proton pump inhibitors) See Figure 1.

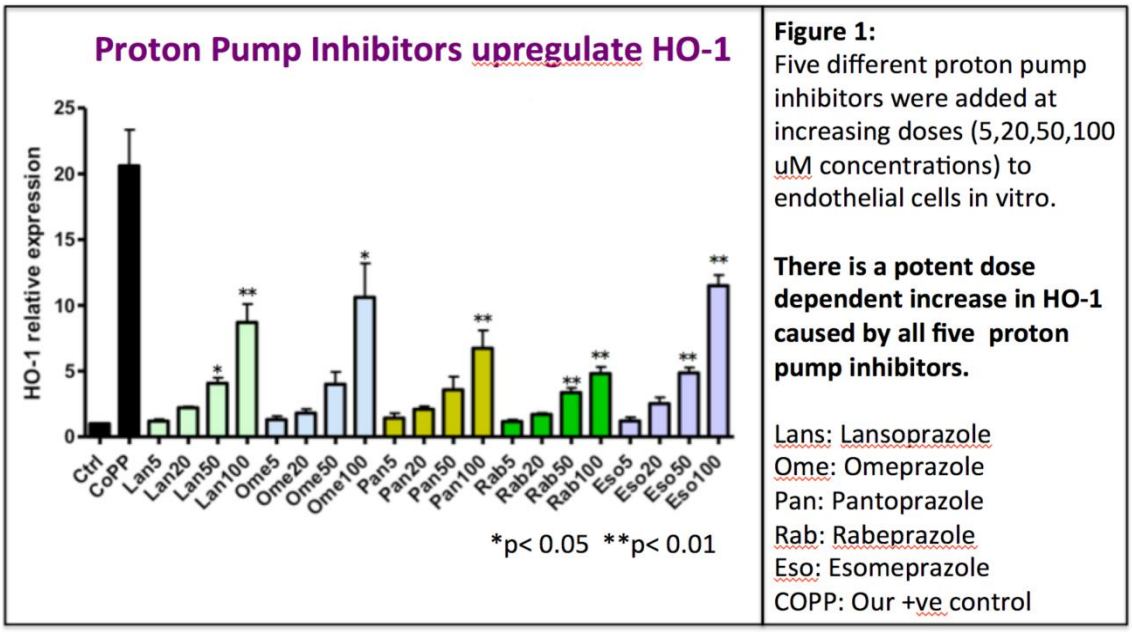


Figure 1: Proton Pump Inhibitors upregulate HO-1

Specifically, esomeprazole was found to have extremely potent effects in inducing HO-1. Esomeprazole induced HO-1 by **11.5 fold** in endothelial (primary HUVEC) cells and **3.9 fold** in purified primary trophoblast cells. See Figure 2.

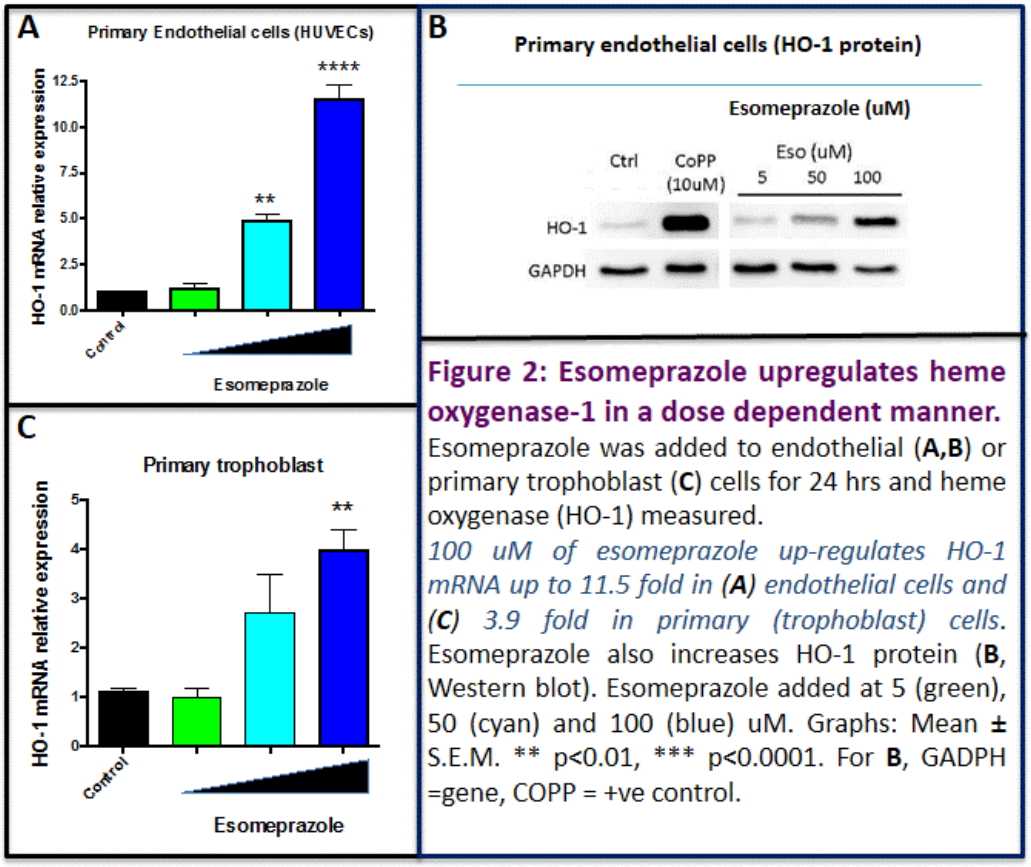


Figure 2: Esomeprazole upregulates heme oxygenase-1 in a dose dependent manner. Esomeprazole was added to endothelial (**A,B**) or primary trophoblast (**C**) cells for 24 hrs and heme oxygenase (HO-1) measured. *100 uM of esomeprazole up-regulates HO-1 mRNA up to 11.5 fold in (**A**) endothelial cells and (**C**) 3.9 fold in primary (trophoblast) cells.* Esomeprazole also increases HO-1 protein (**B**, Western blot). Esomeprazole added at 5 (green), 50 (cyan) and 100 (blue) uM. Graphs: Mean ± S.E.M. ** p<0.01, *** p<0.0001. For **B**, GADPH =gene, COPP = +ve control.

Thus, esomeprazole potently induces the anti-oxidant enzyme HO-1 in both primary human endothelial and trophoblast (placental) cells. This makes it an exciting candidate drug therapy for pre-eclampsia.

Our current hypothesis is that proton pump inhibitors up-regulate HO-1 by increasing the levels of nuclear factor erythroid-derived 2-like 2 (NRF-2). NRF-2 is a transcription factor upstream of HO-1. Once activated, NRF-2 enters the nucleus and activates a host of genes that have anti-oxidant actions, especially HO-1, that up-regulate genes in the oxidative phosphorylation pathway (beneficial to counteract hypoxia). The Translational Obstetrics Group has shown that PPIs induce NRF-2 translocation into the nucleus (data not shown).

NRF-2 is usually bound by Kelch-like ECH-associated protein 1 (KEAP-1) and targeted for degradation. KEAP-1 is a molecular sensor of oxidative stress and also senses other molecules including drugs. While not yet proven in the laboratory, our hypothesis is that KEAP-1 senses PPIs which induce a structural change in KEAP-1. In the new confirmation state, KEAP-1 is less able to

bind and degrade NRF-2. NRF-2, free from KEAP-1, is then able to enter the cells and up-regulate anti-oxidant genes, including HO-1.

2.3.2 Proton pump inhibitors block the release of sFLt-1 and soluble endoglin (sEng)

A major advance in the field of pre-eclampsia was made with the identification of sFlt-1 and sEng as the likely 'toxins' released from the placenta causing the severe maternal organ end-injury seen in pre-eclampsia[20]. Their effect is probably mediated via anti-angiogenic mechanisms.

The evidence implicating sFlt-1 and sEng as central to the pathogenesis of pre-eclampsia is compelling[22]. Serum sFlt-1 and sEng are increased in women with pre-eclampsia many weeks preceding clinical disease and there is a dose dependent relationship between serum levels and disease severity[14]. sFlt-1 administered *in vivo* to pregnant rats can induce hypertension and proteinuria[23]. Impressively, co-administration of both sFlt-1 and sEng in pregnant rats recapitulates the entire spectrum of end-organ injury seen in severe pre-eclampsia[24]. sFlt-1 and sEng are, by far and away, the most studied molecules in the field of pre-eclampsia.

Blocking sFlt-1 and sEng release is therefore a potential therapeutic strategy to treat pre-eclampsia. sFlt-1 and sEng are present in the serum of normal pregnancies, and increase with advancing gestation[14]. Thus, an effective therapeutic may only need to decrease levels and it may not be necessary to completely abolish production altogether.

The acceptance of the strategy to reduce levels of these anti-angiogenic factors as a means to treat pre-eclampsia is highlighted by the design of the 'Statins to Ameliorate early onset Pre-eclampsia' (STAMP) trial[21]. This UK based trial which has been approved by the University of Birmingham seeks to examine the potential of using pravastatin to treat early onset pre-eclampsia, and is the only significant randomised trial of an oral agent to treat early onset pre-eclampsia that we are aware of. The primary outcome of this trial is to show a significant reduction in serum sFlt-1.

The Translational Obstetrics Group has generated preclinical data showing esomeprazole induces marked decreases in sFlt-1 and sEng in both primary endothelial and trophoblast cells (see figure 3). The reductions are extremely potent: the highest dose of esomeprazole of 100

uM decreased sFlt-1 in primary trophoblast by >50% (Fig 3B) and reduced sEng by >90% (Fig 3D).

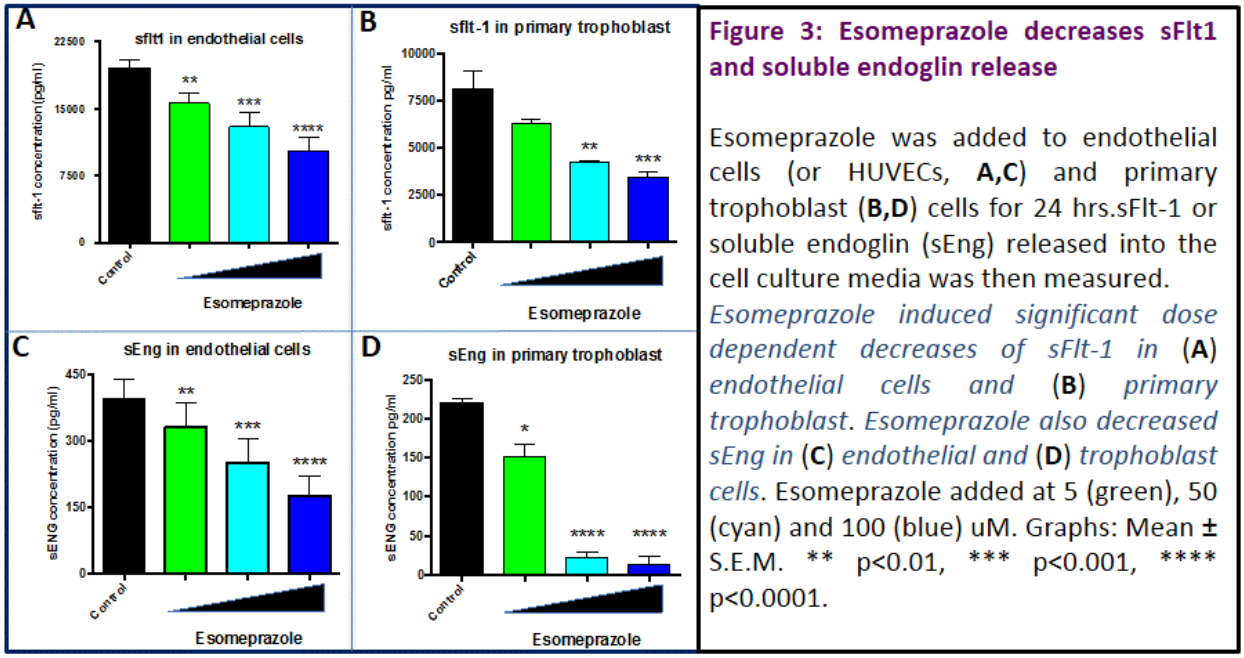


Figure 3: Esomeprazole decreases sFlt1 and soluble endoglin release

Esomeprazole was added to endothelial cells (or HUVECs, **A,C**) and primary trophoblast (**B,D**) cells for 24 hrs.sFlt-1 or soluble endoglin (sEng) released into the cell culture media was then measured. *Esomeprazole induced significant dose dependent decreases of sFlt-1 in* (**A**) *endothelial cells and* (**B**) *primary trophoblast. Esomeprazole also decreased sEng in* (**C**) *endothelial and* (**D**) *trophoblast cells*. Esomeprazole added at 5 (green), 50 (cyan) and 100 (blue) uM. Graphs: Mean ± S.E.M. ** p<0.01, *** p<0.001, **** p<0.0001.

Figure 3: Esomeprazole decreases sFlt1 and soluble endoglin release

To confirm the choice of esomeprazole as the best candidate in the proton pump inhibitor group it was tested against 4 other proton pump inhibitors. The effect on sFlt-1 and soluble endoglin was measured (see figure 4). Esomeprazole again had the most potent dose dependent effect (data still to be published).

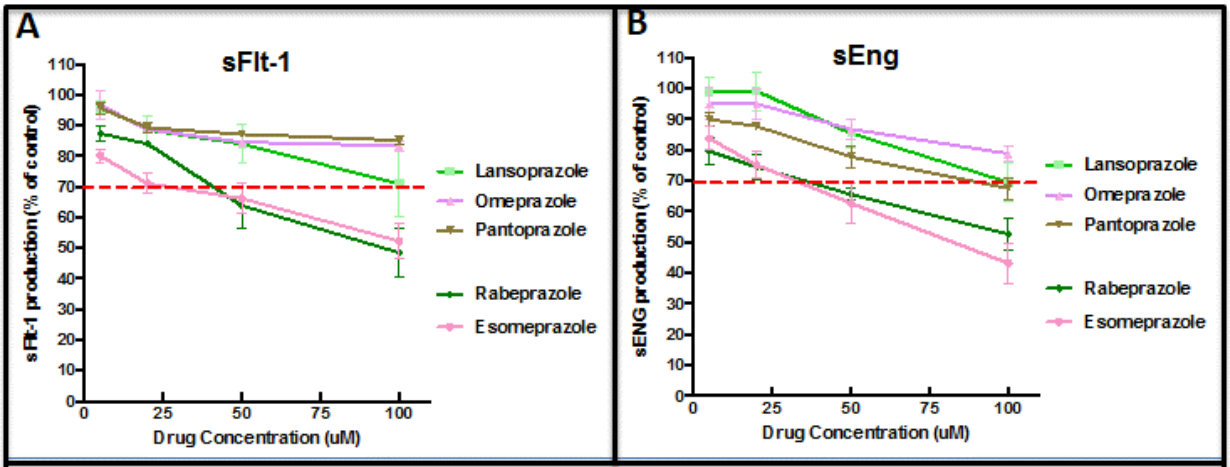


Figure 4: A comparison of five proton pump inhibitors shows esomeprazole is the most potent in reducing sFlt-1 and sEng.

The graphs show sFlt (A) and soluble endoglin (sEng B) levels with different drug concentrations of five different proton pump inhibitors. The red line shows the IC-30, drug concentrations required to decrease either molecule by 30% of control levels.

The graph shows rabeprezole and esomeprazole are the most potent proton pump inhibitors to decrease sFlt-1 and sEng of the five screened.

Experiment done in HUVEC cells, and is the same experimental protocol as the results presented in figure 3A and C.

Figure 4: A comparison of five proton pump inhibitors shows esomeprazole is the most potent in reducing sFlt-1 and sEng.

Pravastatin entered clinical trials on the strength of preclinical data generated from rodent animal models[25-27]. Surprisingly, there has been a lack of published data reporting whether it can reduce sFlt1 and sEng production from human blood vessels and placenta. The Translational Obstetrics Group examined pravastatin using the same assays done for esomeprazole (ie Figure 3). At the same doses used to test the proton pump inhibitors (5, 50, 100 uM), pravastatin had *no effect* on either sFlt-1 or sEng production. Dose response experiments showed that when the pravastatin dose was increased to 2000 UM (20 times the top dose of esomeprazole) sFlt-1 only showed a 30% drop in level and there was actually a dose dependent increase of sEng. Therefore, in functional assays using primary human tissues, esomeprazole appears to considerably outperform pravastatin in potency and desired effect.

Currently, we are not aware of any other candidate drugs in the literature that induce such potent reductions in these anti-angiogenic factors and that decreases both of these anti-angiogenic factors as the proton pump inhibitor group does.

2.3.3 Proton pump inhibitors decrease endothelial dysfunction of blood vessels

A hallmark of pre-eclampsia is endothelial dysfunction, a form of maternal blood vessel injury[20]. It is the likely reason that raised blood pressure is one of the most predictable clinical responses in an illness that is notorious for its varied clinical presentations.

When endothelial dysfunction occurs, the blood vessels express adhesion proteins on the cell surface, principally Vascular Cell Adhesion Molecule -1 (VCAM-1)[28]. VCAM-1 directly binds to leukocytes, causing leukocyte adhesion to the vascular endothelium. With dysfunction, endothelial cells also release endothelin-1, a potent vasoconstrictor, into the circulation. Levels of endothelin-1 are increased with pre-eclampsia[29]. VCAM-1 and endothelin-1 are widely accepted as markers of endothelial dysfunction[28].

The Translational Obstetrics Group has recently found that esomeprazole potently blocks up-regulation of VCAM-1 and endothelin-1 induced by Tumour Necrosis Factor-α (TNF-α), an inflammatory molecule involved in endothelial dysfunction (see Figure 5). The effects were very potent: at the top dose of esomeprazole, VCAM-1 mRNA is undetectable and mRNA of endothelin 1 is reduced by >80% (data still to be published).

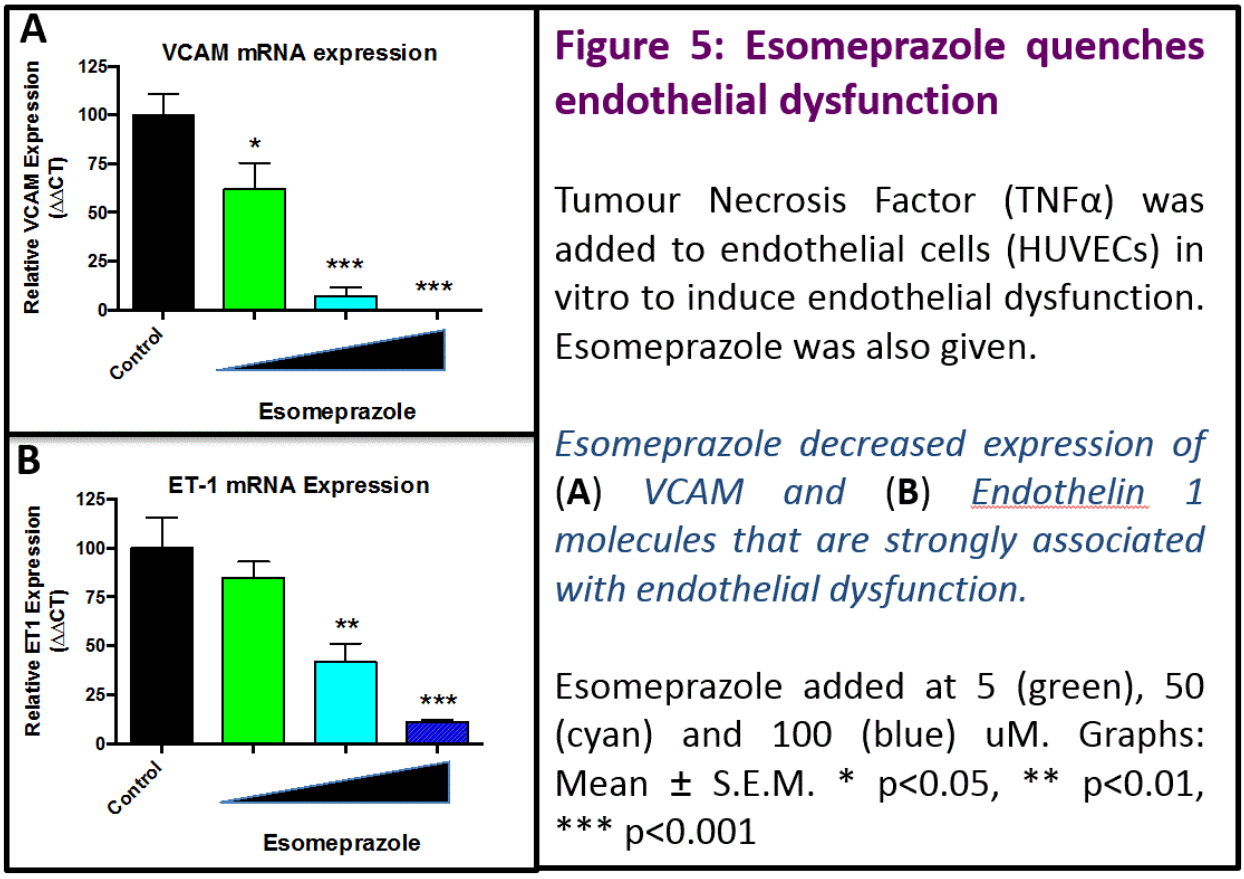


Figure 5: Esomeprazole quenches endothelial dysfunction

Thus, esomeprazole may be able to powerfully quench endothelial dysfunction, a hallmark of pre-eclampsia.

The preclinical evidence presented in this application has been derived from functional studies using primary human tissues, not immortalized cells. *Thus, generated from primary human tissues, this data represents a high level of preclinical evidence*. Secondly, all data presented were derived from the mean of at least three biological replicates (ie each experiment was repeated at least three times). The preclinical data is therefore robust.

2.3.4 Animal Models for pre-eclampsia

Unfortunately pre-eclampsia is a disease that is seen only in humans and there are no convincing animal models of pre-eclampsia.

There are a number of animal models that have been proposed but differences in placentation among mammals make the search for a model that satisfies the criteria of pre-eclampsia a challenge[30]. For instance, for cloven-hoofed mammals such as sheep, normal placental implantation is very shallow. This severely limits their utility to model the poor placental invasion of maternal spiral arteries given normal invasion is already shallow[31]. In non-primate humans like monkeys and baboons the full spectrum of pre-eclampsia has never been reported. Placental implantation of guinea pigs is generally deeper and therefore more similar to humans, but these animals also do not exhibit the signs and symptoms of pre-eclampsia[30,32]. There are some mouse models of pre-eclampsia where the anti-angiogenic factors are inserted into the mice by plasmids and the protein levels artificially over-expressed. While they can recapitulate increased anti-angiogenic factor production, hypertension and even maternal end-organ injury, they are a little less convincing as they do not model shallow placental implantation that is a key pathophysiological step in pre-eclampsia.

Furthermore, we propose esopremazole acts by decreasing oxidative stress, decreasing release of anti-angiogenic factors and decreasing endothelial dysfunction. There is no animal model of preeclampsia that has all three elements of oxidative stress, elevated release of anti-angiogenic factors and endothelial dysfunction.

In summary, studies on pre-eclampsia treatment are limited by the fact that there are no accurate animal models. This makes it extremely difficult to test new medications and doses as initial trials need to be performed on humans to assess applicable doses efficacy.

2.4 Proton Pump inhibitors

2.4.1 Safety data in pregnancy

Proton pump inhibitors have been commonly used in pregnancy to treat gastroesophageal reflux disorders and more serious gastrointestinal complications like Helicobacter pylori-infection, peptic and duodenal ulcers and Zollinger-Ellison syndrome[35].

2.4.1.1 Animal studies:

Reproductive studies have been performed on rats and rabbits, with doses greater than 57 times and 35 times respectively of the human dose of 40mg[36]. These doses have revealed no

evidence of impaired fertility or teratogenicity to the fetus. Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal or greater than 33.6 times an oral human dose of 40mg. (Nexium product information). These changes were reversible after birth.

2.4.1.2 Human studies

Esomeprazole has recently been reclassified as a Category C drug in pregnancy from a Pregnancy Category B drug by the Food and Drug Administration (FDA). Category B is for medications where studies in animals have not shown a risk to the fetus but where adequate data in humans are not available[37]. Category C is for drugs where animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in human, but potential benefits may warrant use of the drug in pregnant women despite potential risks[38].

The reason for changing the classification of esomeprazole was based on the above animal studies where bone changes were noted. In human pregnancies doses equal to 33.6 times the oral human dose of 40mg are never used. There have been no reports of changes in bone morphology in newborns exposed to esomeprazole during pregnancy (Nexium product information).

The Australian categorisation system and database for prescribing medicines in pregnancy classifies esomeprazole as a category B3 drug in pregnancy. A category B3 drug is one that has been taken by a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed and where animal studies have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. (http://www.tga.gov.au/hp/medicines-pregnancy.htm)

One nested case control analysis which suggested a possible link with proton pump inhibitors and septal cardiac birth defects. The authors suggested that this result be confirmed with larger observational studies[39]. Larger observational studies have not proven this to be true.

Large population based cohort studies and systematic reviews (including administration during the first trimester) did not find adverse effects in pregnancy. Specifically, these studies did not find an increased risk of congenital defects or any adverse neonatal outcomes. The most recent systematic literature review published in 2009 included 1530 pregnancies exposed to proton

pump inhibitors and had 133,410 non-exposed matched controls. There was no increase in major congenital abnormalities, no increased risk of spontaneous miscarriages or preterm delivery[35].

The largest study to date, published in 2010, spanned a 13 year period and involved 840,968 pregnancies of which 5082 were exposed to proton pump inhibitors in the first trimester of pregnancy. This study concluded that exposure to proton pump inhibitors, even during the first trimester of pregnancy, was not associated with an increased risk of major birth defects[40]. In 2012, a further large study involving 112 022 pregnancies of which 1 186 pregnancies had been exposed to proton pump inhibitors confirmed there was no associated increase risk for congenital anomalies with proton pump inhibitor use. Importantly this study also found no increase in fetal growth restriction or adverse neonatal outcomes (including premature delivery and low Apgar scores) in pregnancies exposed to proton pump inhibitors in the first, second or third trimesters of pregnancies[41].

Pravastatin has been assigned to pregnancy category X by the FDA and the Australian categorisation system and database for prescribing medicines in pregnancy. The Australian system classifies drugs that have a high risk of causing permanent damage to the fetus as category X. They feel that these drugs should not be used in pregnancy or when there is a possibility of pregnancy. The FDA classifies category X drugs in pregnancy as medications where studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. Despite this, pravastatin has been approved for trials in women with early onset preeclampsia (STAMP trial) and for women at risk of developing preeclampsia. In both of these studies the risk to the mother of early onset preeclampsia was felt to warrant trials with a category X drug.

We are proposing a similar trial design for the same medical condition with a drug where the classification systems state that use may be of benefit in certain clinical situations. Esomeprazole and other proton pump inhibitors have been used in thousands of human pregnancies no increase in fetal growth restriction or adverse neonatal outcomes (including premature delivery and low Apgar scores) in the first, second or third trimesters of pregnancies. We will only be using treatment for a relatively short period in the late second and early third trimesters.

2.4.2 Esomeprazole drug information

Product information on esomeprazole can be found at the following link: *www1.astrazeneca-us.com/pi/Nexium.pdf*

2.4.2.1 Dosage

Esomeprazole is available as delayed-release tablet sachet or capsule for oral administration in two strengths: 20mg and 40mg. The standard dosage for the treatment of gastroesophageal reflux disease is 20 to 40mg once daily. We will be giving our participants a single daily dose of 40mg.

There is currently no pharmacokinetic data available on pregnant women using esomeprazole as they are were excluded from the original phase 1 trials.

We have decided to use the standard dose of 40mg daily (rather than 20mg) after reviewing the available pharmacokinetic data on esomeprazole[42,43]. 40mg provides a longer steady state and better suppression of symptoms. Pregnancy is associated with haemodilution and for this reason 40mg may already result in lower levels than in non-pregnant women. As such, we would be concerned 20mg could be less efficacious given the haemodilution seen in pregnancy.

Notably, 40mg is a dose that has been used in pregnancy in the late second and third trimester. This dose appears adequate in providing substantial symptomatic relief from reflux implying it results in adequate maternal circulation drug levels and an efficacious therapeutic response. Critically, large cohort studies (equivalent to post-marketing surveillance data done in large populations after the release of any drug) did not find this drug to be associated with adverse effects among pregnant women.

We do not feel comfortable using higher dosages as there is no published data examining the safety of higher doses have in pregnancy. Furthermore, given there are no adequate animal models of pre-eclampsia, we cannot use in vivo animal models to guide us in deciding whether an alternative dose other than 40mg is more appropriate.

If esomeprazole was proven to be a treatment option for pre-eclampsia, then we have the option then of instigating further larger multicentre trials to test different doses. Currently it is not pragmatically viable for us to do a multiarm study examining different doses given the numbers needed would be prohibitively large.

2.4.2.2 Contraindications

Esomeprazole is contraindicated in patients who have a known hypersensitivity to proton pump inhibitors. For this reason a previous hypersensitivity reaction to proton pump inhibitors will be an exclusion criterion for the study.

2.4.2.3 Warnings and precautions

There may be a small risk of clostridium difficile associated diarrhoea in severely ill patients. Our participants will be closely monitored for any effects of the medication and if significant diarrhoea develops the trial nurse will urgently notify the attending clinician and will inform them of the potential risk of clostridium difficile associated diarrhoea.

2.4.2.4 Adverse reactions

The most common adverse reactions in adults are headache, diarrhoea, nausea, flatulence, abdominal pain, constipation and a dry mouth. Caution will be exercised as some of these symptoms overlap with those of pre-eclampsia. All participants will be given an information sheet about all the possible effects of esomeprazole.

2.4.2.5 Drug interactions

Antiretroviral drugs

Decreased serum levels of the antiretroviral drugs atazanavir and nelfinavir have been reported with the use of omeprazole. This could lead to antiretroviral drug resistance and concomitant use is therefore not recommended. Increased serum levels have been reported with the concomitant use of omeprazole with saquinavir. A decrease in the dose of saquinavir may be indicated if used together. For these reasons, women using the above antiretroviral medication will be ineligible for our study.

Drugs for which gastric pH can affect bioavailability

Esomeprazole inhibits gastric acid secretion so the absorption of drugs such as digoxin may increase with concomitant use and the absorption of drugs such as ketoconazole and iron salts may be decreased.

Women using digoxin and ketoconazole will be excluded from the study. Most pregnant women with anaemia at Tygerberg Hospital are treated with iron salts. We will therefore monitor haemoglobin levels to ensure anaemia is not developing due to a lack of iron absorption potentially caused by esomeprazole.

Effects on hepatic metabolism

Esomeprazole is metabolised by the CYP 2C19 and CYP 3A4 pathways in the liver.
It can potentially interfere with the CYP 2C19 pathway and may result in a decreased clearance of diazepam, estimated to be a 45% decrease. If a mother is using diazepam she will not be eligible for the study.

Clopidogrel is an antiplatelet agent that is partially metabolised to its active agent by the CYP2C19 pathway. Therefore the concomitant use of esomeprazole with clopidogrel should be avoided as esomeprazole decreases the activity. Clopidogrel is rarely used in pregnancy. However, if a mother is on this treatment she will not be eligible for the study.

Drugs known to induce the CYP2C19 or CYP3A4 pathways like St John's Wort or rifampicin can substantially decrease esomeprazole concentrations and should not be used in combination with esomeprazole. The use of these medications will be an exclusion criterion.

Effects on renal impairment

Data is limited in patients with impaired renal function, but patients will be delivered before significantly elevated levels of serum creatinine are reached.

Other medications

The use of the following medications will be an exclusion criterion for this study since esomeprazole may affect their bioavailability:

- Warfarin
- Voriconazole
- Cilostazol
- Tacrolimus
- Erlotinib
- Methotrexate

These medications are not generally used in pregnancy.

2.4.2.6 Mechanism of action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase in the gastric parietal cell.

As discussed, esomeprazole appears to 1) up regulate HO-1 2) decrease production of sFlt-1 and sEng and 3) decrease markers of endothelial dysfunction in endothelial cells. We have yet to elucidate the exact molecular target that esomeprazole directly interacts with to elicit these

changes. However, they are likely to be independent to its effects that cause proton pump inhibition.

As noted above, we postulate the up regulation of HO-1 may be mediated through a direct interaction of esomeprazole and KEAP-1. This releases NRF-2 which translocates to the nucleus and up regulates a raft of genes (including HO-1) involved in anti-oxidant defences.

2.4.2.7 Pharmacokinetics

Esomeprazole is 97% bound to plasma proteins and is metabolised by the liver. The metabolites lack antisecretory activity. The plasma elimination half-life is about one to one and a half hours. Less than 1% of the parent drug is excreted in the urine with 80% being excreted as inactive metabolites in the urine and the rest excreted as inactive metabolites in the faeces.

2.5 Summary

Currently, the only option for the treatment of pre-eclampsia is delivery. At extremely premature gestations this subjects the neonate to the risk of significant morbidity and mortality.

Preclinical data has uncovered potent biological actions suggesting esomeprazole may be a lead candidate therapeutic to treat pre-eclampsia**.** Treatment with a proton pump inhibitor in the late second trimester or early third trimester, which is well after organogenesis has occurred, for a relatively short period, is likely to have a negligible risk of causing fetal anomalies and adverse perinatal outcomes.

We have commenced a unique collaboration between Stellenbosch and Melbourne University that will allow us to test this hypothesis in Tygerberg Academic Hospital, South Africa. This population has a high prevalence of early onset pre-eclampsia. A trial of similar size in the developed world would require much larger numbers of participating sites.

3.0 Aims and Objectives

3.1 Specific Aims and Outcomes:

Primary aim:

1) To examine whether a single daily dose of 40 mg of esomeprazole can safely prolong gestation for an additional 5 days in women with early onset pre-eclampsia diagnosed 26+0 – 31+6 weeks who are being managed expectantly compared to expectant management alone.

Primary outcome:

1) Prolongation of gestation measured from the time of enrolment to the time of delivery, in hours and days.

Secondary aims:

2) To determine whether esomeprazole can improve 1) maternal 2) fetal and 3) neonatal outcomes in early onset pre-eclampsia being managed expectantly compared to expectant management alone.
3) To examine whether 40 mg of daily esomeprazole can significantly decrease levels of circulating sFlt-1 and/or sEng in women with early onset pre-eclampsia who are being managed expectantly compared to expectant management alone.
4) To examine whether 40 mg of daily esomeprazole is safe and well tolerated in the mother and infant, compared with placebo.

3.2 Hypothesis

Primary Hypothesis:

1) 40 mg of daily oral esomeprazole can safely prolong gestation for at least a further 5 days in women with early onset pre-eclampsia diagnosed between 26+0 – 31+6 weeks, compared to expectant management alone.

Other hypotheses:

2) 40 mg of daily oral esomeprazole can improve maternal, fetal and neonatal outcomes, in women diagnosed with early onset preeclampsia, compared to expectant management alone.
3) 40 mg of daily oral esomeprazole can significantly decrease the circulating levels of sFlt1 and sEng in early onset preeclampsia being managed expectantly compared to expectant management alone.

4) 40 mg of daily oral esomeprazole is safe and well tolerated in the mother, fetus and infant.

4.0 Study Design

4.1 Type of study

Hospital based phase II placebo-controlled, double-blind parallel randomised control trial.

To classify the phase of this study is somewhat difficult given esomeprazole is already an approved drug. Historically pregnant women and children have been excluded from all phase 1 trials as they do not fall under the category of “healthy volunteers”. This makes any trial in pregnant women more difficult. Furthermore, phase I trials are typical those where the primary outcome is safety. There already has been very large cohort studies to suggest 40mg of esomeprazole in pregnancy women is safe.

We have classified this trial as a phase 2 trial as we will be assessing efficacy and safety. We aim to determine whether esomeprazole is effective for the treatment of pre-eclampsia.

4.2 Study population

Pregnant women diagnosed with early onset pre-eclampsia at a gestational age between 26+0 weeks to 31+6 weeks who qualify for expectant management. All who consent and meet eligibility criteria will be enrolled in the study.

4.3 Intervention

Participants will be randomised to daily administration of either active tablets containing 40 mg of esomeprazole or an identical placebo tablet. The study will not alter or interfere with any treatment or care given routinely to women with early onset pre-eclampsia. A single dose of 40 mg will be given orally once a day.

4.4 Sample size calculations

The primary outcome will be to determine whether treatment with esomeprazole can result in a gain in length of gestation.

In the largest descriptive study on expectant management of early onset pre-eclampsia Hall, et al., described the length of gestation gained by such management before delivery[44]. Importantly, this retrospective study was performed at the same hospital where we plan to run this trial (Tygerberg Hospital) and clinical practice regarding expectant management is well organised, and has not significantly changed since that landmark publication. Thus, it provides valuable data with which to base a power calculation for the present study. The reported duration that fetuses remained in utero after diagnosis and admission of pregnancies complicated by early onset pre-eclampsia was a mean of 11 days (with a standard deviation of 7 days) and a median 9 days (range of 1 to 47 days)[44].

We believe an intervention that allows a gain in gestation of a further 5 days would be a clinically important difference and likely to have important beneficial implications for the fetus (although perinatal outcomes will not be a primary outcome in this phase II study).

For 90% power, with a two-sided alpha set of 0.05, 43 patients are required in each group (table 1) to identify a gain in gestation of 5 days. Given the data reported by Hall et al was skewed, we multiplied this by 1.15 to make a statistical allowance for non-normality[45]. This increases the numbers to 50 per arm (43x1.15). We will add an additional 10 per arm to allow for drop-outs, which equates to 60 per arm. *Thus, a total of 120 participants will be recruited to provide sufficient power to examine our primary outcome.*

Table 1: Sample size calculation

Detectable difference (in days)	Group size, per arm	Group size x 1.15*
3	116	134
4	66	76
5	43	50
6	30	35
7	23	27

* The reason for expanding the group size by 15% is that the data in the Hall paper is skewed and not normally distributed. The inflation of the sample size by 15% provides an adjustment that makes an allowance for non-normality[45].

(Power calculation Performed using PASS 12 software. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA)

The gestational age at diagnosis is likely to affect allowable length of pregnancy prolongation. For instance, those diagnosed at 31+6 will be delivered at 34 weeks (should they reach that

gestation), as it is unit policy to deliver at that gestation. Thus, such patients will have a maximum length of pregnancy prolongation of 15 days. In contrast, those diagnosed at 28 could conceivably obtain many weeks of pregnancy prolongation (if the disease remains stabilised). Further it is possible that esomeprazole efficacy may vary with gestational age at diagnosis.

To ensure treatment group allocation is balanced for this potential variable, we will stratify randomisation into strata based on gestational age.

	Gestational age (GA)	**EFW if GA is unknown**
Strata 1	26 +0 up to and including 28+6 weeks	Less than and including 1100gm
Strata 2	29+0 up to and including 31+6	Greater than 1100gm

Stratified randomisation will ensure that the number of participants in each gestational age strata is balanced.

4.5 Randomisation and allocation concealment

Randomisation will be done in an equal ratio of esomeprazole to placebo. An online, web-based sequence generator system will be used to avoid chance imbalances in the stratification process. It will be linked with codes for placebo and treatment tablets provided by the manufacturer contracted to produce the trial medication. Researchers and participants will both be blinded.

Randomization will include blocking within each stratum. Blocking ensures that the control and treatment group numbers remain close both within the strata and overall. We propose using blocks of 4 to 6 with the size and order randomly assigned. Its use of stratified randomization ensures balance between treatment and control groups for gestational age however its use induces within stratum induces correlation. We will take this into account in the analysis by treating strata as a covariates in regression analysis or as levels in Mantel-Haenszel pooled treatment effects.

Once the participants have been randomised the treatment pack with the same code will be allocated to the participant. All treatment packs will be identical and will contain either active tablets or placebo. The treatment packs will be prepared by the manufacturer contracted to produce the trial medication. The researchers will have no access to the randomisation list. This process will ensure that there is allocation concealment throughout the conduct of the trial. The allocation will only be released once the trial is completed.

5.0 Inclusion and exclusion criteria

5.1 Definitions:

There are many classification systems for the hypertensive disorders of pregnancy. The International Society for the Study of Hypertensive Disorders in Pregnancy (ISSHP) has recently published a new classification system for hypertensive disorders in pregnancy[46]. We will use this classification system in this study.

The following definitions are used in this classification system:

Hypertension in pregnancy: office or in hospital systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Severe Hypertension: systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Pre-existing (chronic) hypertension: hypertension that pre-dates the pregnancy or appears before 20 weeks gestation.

Gestational Hypertension: hypertension that appears at or after 20 weeks of gestation.

Pre-eclampsia: gestational hypertension and new proteinuria or one or more adverse conditions or one or more serious complications (see table 3 for definitions of adverse conditions and serious complications).

Adverse condition: consists of maternal symptoms, signs, abnormal laboratory results and abnormal fetal monitoring that may herald the development of severe maternal or fetal complications.

Significant proteinuria: greater than or equal to 0,3 g/d in a complete 24-hour urine collection or a spot (random) urine sample with greater than or equal to 30 mg/mmol urinary creatinine.

Severe pre-eclampsia: pre-eclampsia associated with a severe complication that warrants delivery regardless of gestational age.

Table 2: ISSHP classification of hypertensive disorders in pregnancy[46]

Classification of the HDP.

	Comments
Pre-existing (chronic) hypertension	This is defined as hypertension that was present either pre-pregnancy or that develops at <20^0 weeks gestation
• With comorbid condition(s)	Comorbid conditions (e.g., pre-gestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
• With evidence of preeclampsia	This is also known as 'superimposed preeclampsia' and is defined by the development of one or more of the following at ⩾ 20 weeks: • Resistant hypertension, *or* • New or worsening proteinuria, *or* • One/more adverse condition(s) *or* • One/more severe complication(s) Severe preeclampsia is defined as preeclampsia with one or more severe complication(s)
Gestational hypertension	This is defined as hypertension that develops for the first time at ⩾ 20^0 weeks' gestation
• With comorbid condition(s)	Comorbid conditions (e.g., pregestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
• With evidence of preeclampsia	Evidence of preeclampsia may appear many weeks after the onset of gestational hypertension. Preeclampsia is defined by gestational hypertension and one or more of the following: • New proteinuria, *or* • One/more adverse condition(s) *or* • One/more severe complication(s) Severe preeclampsia is defined as preeclampsia with one or more severe complication(s)
Preeclampsia	Preeclampsia may arise *de novo*. It is defined by gestational hypertension and one or more of the following: • New proteinuria, *or* • One/more adverse condition(s) *or* • One/more severe complication(s) Severe preeclampsia is defined as preeclampsia with one or more severe complications[v]
'Other hypertensive effects'*	
Transient hypertensive effect	Elevated BP may be due to environmental stimuli or the pain of labour, for example
White coat hypertensive effect	BP that is elevated in the office (sBP ⩾ 140 mmHg or dBP ⩾ 90 mmHg) but is consistently normal outside of the office (<135/85 mmHg) by ABPM or HBPM
Masked hypertensive effect	BP that is consistently normal in the office (sBP < 140 mmHg or dBP < 90 mmHg) but is elevated outside of the office (⩾135/85 mmHg) by ABPM or repeated HBPM

ABPM, ambulatory BP monitoring; BP, blood pressure; HBPM, home BP monitoring.
* These may occur in women whose BP is elevated at <20^0 or ⩾20^0 weeks who are suspected of having pre-existing or gestational hypertension/preeclampsia, respectively.

Table 3: ISSHP classification of adverse conditions and severe complications of preeclampsia[39]

Adverse conditions and severe complications of preeclampsia.

Organ system affected	Adverse conditions (that increase the risk of severe complications)	Severe complications (that warrant delivery)
CNS	○ Headache/visual symptoms	○ Eclampsia ○ PRES ○ Cortical blindness or retinal detachment ○ Glasgow coma scale < 13 ○ Stroke, TIA, or RIND
Cardiorespiratory	○ Chest pain/dyspnoea ○ Oxygen saturation < 97%	○ Uncontrolled severe hypertension (over a period of 12hr despite use of three antihypertensive agents), ○ Oxygen saturation < 90%, need for ⩾ 50% oxygen for > 1hr, intubation (other than for Caesarean section), pulmonary oedema ○ Positive inotropic support ○ Myocardial ischaemia or infarction
Haematological	○ Elevated WBC count ○ Elevated INR or aPTT ○ Low platelet count	○ Platelet count < $50x10^9$/L ○ Transfusion of any blood product
Renal	○ Elevated serum creatinine ○ Elevated serum uric acid	○ Acute kidney injury (creatinine > 150 μM with no prior renal disease) ○ New indication for dialysis
Hepatic	○ Nausea or vomiting ○ RUQ or epigastric pain ○ Elevated serum AST, ALT, LDH, or bilirubin ○ Low plasma albumin	○ Hepatic dysfunction (INR > 2 in absence of DIC or warfarin) ○ Hepatic haematoma or rupture
Feto-placental	○ Non-reassuring FHR ○ IUGR ○ Oligohydramnios ○ Absent or reversed end-diastolic flow by Doppler velocimetry	○ Abruption with evidence of maternal or fetal compromise ○ Reverse ductus venosus A wave ○ Stillbirth

AST, aspartate aminotransferase; ALT, alanine aminotransferase; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible neurological deficit < 48hr; RUQ, right upper quadrant; TIA, transient ischaemic attack.

A number of patients seen at Tygerberg Hospital only book after a gestational age of 20 weeks. The ISSHP classification systems does not have a class for these patients. We will classify these patients according to the classification of Davey and MacGillivray[47].

Unclassified proteinuric hypertension:
Hypertension and proteinuria diagnosed in a patient who is seen for the first time after 20 weeks of gestation.

We will then contact these patients 6 weeks postpartum to determine whether their blood pressure has normalized or not and will then retrospectively reclassify them as either as pre-eclampsia or chronic hypertension with superimposed pre-eclampsia.

5.2 Inclusion criteria

A diagnosis of pre-eclampsia, gestational hypertension with evidence of preeclampsia, preexisting hypertension with evidence of pre-eclampsia or unclassified proteinuric hypertension has been made by the attending clinician who is of the opinion that the patient and fetus would benefit from expectant management.

AND all of the following is present:

- Gestational age between 26 + 0 weeks and 31 + 6 weeks
- Estimated fetal weight by ultrasound between 500gm and 1800 gm (if gestation is not certain)
- Singleton pregnancy
- The managing clinicians have made the assessment to proceed with expectant management and that delivery is not expected within 48 hours
- The managing clinician and neonatologist believe that the fetus could potentially be delivered in a viable condition

ALSO:

- No suspicions of a major fetal anomaly or malformation. A major fetal anomaly is defined as anomalies or malformations that create significant medical problems for the patient or that require specific surgical or medical management. Major anomalies or malformations are not considered a variation of the normal spectrum.
- The mother must be able to understand the information provided, with the use of an interpreter if needed
- The mother must be able to give informed consent
- Patient will be admitted to hospital for expectant management and standardised care

5.3 Exclusion criteria

- Patient is unable or unwilling to give consent
- Established fetal compromise that necessitates delivery. This will be decided by the clinical team before expectant management is offered to the patient.
- The presence of any of the following at presentation:
  - Eclampsia defined as the new onset of grand mal seizure activity and/or an unexplained coma during pregnancy with signs or symptoms of pre-eclampsia[48].
  - Severe hypertension defined as a systolic blood pressure greater than or equal to 160 mmHg or diastolic blood pressure greater than or equal to 110 mmHg that cannot be controlled with antihypertensive medication within 48 hours of admission.
  - Cerebrovascular event defined as an ischaemic or haemorrhagic stroke associated with clinical symptoms and definitive signs on imaging.

  - Posterior reversible encephalopathy syndrome (PRES) associated with pre-eclampsia defined on imaging as reversible vasogenic oedema, usually in the occipital or parietal lobes.
  - Severe renal impairment with a creatinine level of greater or equal to 125 µmol/l or a need for dialysis.
  - Signs of left ventricular failure which include pulmonary oedema requiring treatment or oxygen saturations of less than 90% caused by left sided heart failure.
  - Disseminated intravascular coagulation defined as an INR greater than 2
  - Platelet count at presentation less than $50x10^9$ (platelet aggregation excluded)
  - Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome defined as a platelet count less than 100×10^9/L, aspartate aminotransferase greater than 60 µ/L, and haemolysis as demonstrated by lactate dehydrogenase > 600 µ/L or haemolysis on a peripheral blood smear or a raised haptoglobin level)
  - Liver transaminases greater than or equal to 500IU/L
  - Liver haematoma or rupture
  - Fetal distress on cardiotocography
  - Severe ascites on ultrasound as defined by the sonographer
- Contra-indications for expectant management of pre-eclampsia
- Current use of a proton pump inhibitor
- Contraindications to the use of a proton pump inhibitor
  - Previous hypersensitivity reaction to a proton pump inhibitor
- Current use of a drug that may be affected by a proton pump inhibitor: warfarin, ketoconazole, voriconazole, atazanavir, nelfinavir, saquinavir, digoxin, St John's Wort, rifampin, cilostazol, diazepam, tacrolimus, erlotinib, methotrexate and clopidogrel.

6.0 Outcomes

6.1 Primary outcome

Prolongation of gestation measured from the time of enrolment to the time of delivery, in hours and days.

6.2 Secondary outcomes

Maternal:

- (Composite outcome) The occurrence of any of the following serious maternal outcomes:
  - Maternal death
  - Eclampsia
  - Pulmonary oedema (oxygen saturation ≤90%, with clinical signs and symptoms requiring treatment)
  - Severe renal impairment or the need for dialysis
  - Cerebral vascular event
  - Liver haematoma or rupture

- Other maternal outcomes, where all of the following will be compared as individual outcomes:
  - Admission to a high care or intensive care unit
  - Posterior reversible encephalopathy syndrome (diagnosed on imaging)
  - Left ventricular failure (diagnosed on echocardiography)
  - Serum creatinine greater than or equal to 125 µmol/l
  - Proteinuria greater than or equal to 3g/24h
  - Hypertension with a systolic blood pressure greater than 160mmHg or a diastolic blood pressure greater than 110mmHg despite anti-hypertensive treatment
  - Disseminated intravascular coagulation
  - Platelet count less than $50x10^9$
  - Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome defined as a platelet count less than 100×10^9/L, aspartate aminotransferase greater than 60 µ/L, and haemolysis as demonstrated by lactate dehydrogenase greater than or equal to 600 µ/L or haemolysis on a peripheral blood smear or a raised haptoglobin level)
  - Liver transaminases >500IU/L

- Placental abruption defined as a retroplacental clot covering more than 15% of the maternal surface or a diagnosis on histology
- Mode of delivery
- Use of antihypertensive agents (number of agents and daily dose at delivery)
- Major postpartum haemorrhage (defined as blood loss of more than 1000mls in 24 hours)
- Thromboembolic disease (defined as a deep-vein thrombosis , pulmonary embolism or both)
- Moderate or severe ascites noted on ultrasound or at delivery

Fetal:

(Composite outcome) The occurrence of any of the following serious fetal outcomes:

- Reversed a-wave in the ductus venosus on fetal ultrasound
- Significant changes in heart rate patterns on the non-stress test or cardiotocograph, as defined by the attending clinician, that necessitate delivery
- Intrauterine fetal demise
- Incidence of fetal growth restriction at birth as defined by growth charts based on the local population
- Persistent reversed flow in the umbilical artery confirmed on two fetal ultrasounds
- Redistribution in the middle cerebral artery

There is no standard classification system for the non-stress test. The attending clinician usually assess the heart rate patterns by looking at the baseline, assessing for baseline shifts, by assessing the variability, by looking at the presence or absence of accelerations and the presence of decelerations and by assessing for a sinusoidal pattern. The gestational age of the fetus is also taken into consideration when assessing the non-stress test. The Royal College of Obstetricians and Gynaecologists Evidence-based Clinical guideline Number 8 on electronic monitoring is routinely used at Tygerberg hospital for and will be used by the attending clinician to assess the cardiotocograph. (www.nice.org.uk/nicemedia/pdf/efmguidelinercog.pdf)

Neonatal:

Composite outcome) The occurrence of any of the following serious neonatal outcomes:

- Neonatal death within 6 weeks after the due date
- Grade III or IV intraventricular haemorrhage defined on imaging as enlarged ventricles associated with haemorrhage or when the haemorrhage extends into the cerebral tissue around the ventricles
- Necrotizing enterocolitis diagnosed on radiographic studies

- Bronchopulmonary dysplasia defined as needing oxygen at day 28 of life, either on a ventilator, by CPAP or via a nasal catheter and significant neonatal sepsis as defined by the attending paediatrician.

Other neonatal outcomes, where all of the following will be compared as individual outcomes:

- APGAR score of less than 7 at 5 minutes
- Umbilical artery pH below 7.05
- Umbilical artery lactate
- Surfactant use
- Neonatal intensive care admission or special care unit admission
- Intubation and mechanical ventilation or continuous positive airway pressure (CPAP) support
- Grade III/IV hyaline membrane disease
- Length of oxygen treatment
- Hospital stay
- Incidence of retinopathy of prematurity
- Early neonatal sepsis (Haematological infection diagnosed on blood culture with associated clinical findings or as defined by attending paediatrician)

Biomarkers:

We will ship the following samples from Tygerberg Hospital to The Mercy Hospital, where the following assays will be done (by researchers blinded to clinical groupings) in the Translational Obstetrics Laboratory at Melbourne University if consent has been given by the mother.

- Maternal plasma samples: sFlt1, sEng, endothelin 1 and esomeprazole levels.
- Placental samples: mRNA and protein expression of HO-1, sFlt1 and endothelin 1.
- Immunohistochemistry will be also performed for these same molecules.
- Umbilical cord plasma obtained delivery: esomeprazole levels.

7.0 Trial conduct

7.1 Identification and enrolment of participants

7.1.1 Identification

Potential participants will be identified after they have been admitted to Tygerberg Hospital (tertiary referral centre) with a diagnosis of early onset pre-eclampsia. The clinical management team will decide if the patient qualifies for expectant management and is suitable for admission as per the hospital protocol (potentially can be recruited), or delivery is likely to be imminent within 48 hours (exclusion criteria). The research midwife and principal investigator will be notified by the ward staff and/or clinical treating team.

Normal clinical care will be maintained throughout the study. The use of steroids and magnesium sulphate will be according to local protocols and will be decided upon by the managing clinician. The use of aspirin and calcium will be noted.

Inclusion and exclusion criteria will be assessed before approaching the patient.

7.1.2 Consent

Information about the trial will be given to the patient and a translator (working from a script) will be used if necessary. Information sheets and study details will be given to the patient and any questions about the study will be answered. A translator will be used so the patient will have the opportunity to go through the information in their own language. If they would like to be involved in the study they will be asked to provide written informed consent. The consent form will be made available on self-duplicating paper in order that a signed copy can be given to the participant, a copy can be put in the clinical notes and a copy kept by the study investigators. The consent forms will be translated into English, Afrikaans and Xhosa. Only the study investigators and research midwives will be able to take consent. The patient will be given as much time as they need to decide whether they would like to be involved. Once the participant has signed consent they will be enrolled in the study.

7.1.3 Recruitment

Once the eligibility criteria have been checked and the informed consent document has been signed we will obtain the following:

- Baseline clinical information regarding the pregnancy (maternal age, parity, obstetric history, antenatal history, medical history, drug history, allergies, smoking status, alcohol and drug intake)
- Baseline information
  - Degree of proteinuria (24 hour protein excretion)
  - Maternal assessment (renal function, liver function, blood count)
  - Fetal assessment with ultrasound (biometry, estimated fetal weight, Doppler and amniotic fluid index findings)

7.2 Study treatment

5.2.1 Trial drug

After randomisation an individual treatment pack will be allocated to the participant according to an online web-based randomisation process. The participant will be allocated an individual trial number. The participant's name and trial number will be written on the pack. The packs will be identical in shape, colour, weight and feel. Each pack will contain proton pump inhibitor tablets or identical placebo tablets.

7.2.2 Packaging, formulation and supply of the treatment

The trial drug and placebo will be produced by a contracted manufacturer IDT pharmaceuticals (http://en.idtaus.com.au). The trial drugs will be placed into containers and labelled randomly according to the computer generated randomisation list. Labelling, storage and preparation will be done according to the requirements of the Medicines for Human Use (Clinical Trials) regulations. The placebo will undergo a placebo analysis before the trial is started to confirm the contents.

7.2.3 Route of administration, dosage regimen and treatment period

Each participant will be given a treatment pack. The treatment pack will contain treatment for 21 days. A single capsule will be taken, once daily one hour before meals (if the patient is eating). On the first day of randomisation the first dose will be taken in the evening. Treatment will then be taken daily in the evening until the pregnancy has ended. Trial drugs will be kept in the packaging they are provided in and under no circumstances will it be used for other participants.

The trial medication will be written up on the treatment chart and the chart will be signed by the nursing staff to confirm that the participant has taken the medication and to confirm compliance. The research midwife will monitor the treatment chart to assure compliance. As a second compliance check the patient will be asked return the empty packaging to the research midwife who will record the number of empty tablet containers at the time of delivery of the patient.

7.2.4 Resupply of treatment

It is assumed that for most patients, delivery will occur within 21 days of randomisation. However in some cases delivery may occur after 21 days of randomisation. In these cases continuation trial drug packs will be available. In these cases the principal investigator will contact the randomisation office and ask for a number for a continuation pack. The continuation pack will be matched to the contents of the initial treatment pack and will contain a further 21 day supply of the treatment.

7.3 Expectant management for pre-eclampsia

7.3.1 Routine management

Expectant management for early onset pre-eclampsia involves admission to hospital, and close maternal and fetal surveillance.

Maternal surveillance includes four hourly blood pressure measurement, twice daily clinical assessment, daily urinalysis, and twice weekly assessments with blood tests (full blood count, renal function tests and hepatocellular enzymes if HELLP syndrome is suspected) and 24 hour urinary protein measurement on admission.

Fetal surveillance includes six-hourly cardiotocography and ultrasound assessments every two weeks (or more frequently if clinically indicated) for Doppler velocimetry of the umbilical artery, middle cerebral artery, ductus venosus, amniotic fluid volume assessment and growth.

All participants will receive two doses of betamethasone 24 hours apart to reduce the risks of neonatal respiratory distress syndrome, intracranial haemorrhage and necrotising enterocolitis. A single repeat dose is usually given one week later.

Most participants will be on antihypertensive treatment and the medication used will be documented. All women should already be receiving iron and folic acid supplementation.

Clinical care will be left up to the discretion of the clinical team. The indication for delivery will be a clinical decision. Indications for delivery may include failure to control blood pressure, the development of major maternal or fetal complications, or intrauterine fetal death. Expectant management will usually end at a gestation of 34 weeks.

7.4 Clinical Follow-up

7.4.1 Baseline clinical information

Baseline clinical information collected will include maternal age, gravidity and parity, gestation, obstetric history, antenatal history, medical and surgical history, medication history, allergies, smoking status, alcohol and drug intake, height, weight and body mass index. A photocopy of the antenatal notes will be made and stored with the data capture sheets.

Ongoing clinical data will be collected daily on data capture sheets. This will include clinical measurements, medications, haematological parameters, biochemical parameters, fetal ultrasound and fetal heart rate assessments. Patient folders will be reviewed after delivery to confirm that the data collected is complete and accurate. Once the patient has delivered the folder will be photocopied to assure that all the data is recorded.

7.5 Sample collection

7.5.1 Blood samples

Blood samples are taken as part of routine clinical care (twice a week). These include measurements of the haemoglobin, the platelet count and the urea and creatinine levels. If HELLP syndrome is suspected the hepatocellular enzymes are measured and a coagulation profile may be ordered. We will collect an extra 9 mls of blood each time routine bloods are taken to obtain plasma samples. These will be processed immediately and frozen at -80°C for later analysis of sFlt, sEng, and endothelin 1. In addition, all participants we undergo the following test once*:* we will precisely time blood sampling 2 hours after taking the trial medication where we will measure plasma esomeprazole levels.

Tubes will be labelled with the participant's trial number and folder number. The samples will be spun, and split into two aliquots. One aliquot will be used to measure sFlt-1 and sEng. The laboratory doing the measurement of sFlt-1 and s-Eng will be confirmed closer to the start of the trial. The other aliquot will be stored in a -80 degree freezer and sent to Melbourne University for analysis and will be analysed in the Translational Obstetrics Laboratory.

We plan to measure the following in the blood samples:

- ***Biomarkers of endothelial injury***: endothelin 1 and inflammatory cytokines
- ***Antiangiogenic factors associated with pre-eclampsia:*** sFlt1 and soluble endoglin
- ***Esomeprazole levels in the blood***
- The samples sent to Melbourne may be used to measure other relevant analytes associated with pre-eclampsia. No genetic testing will be performed on these samples.

The purpose of these blood analyses is to have more objective (and scientifically robust) evidence of maternal disease regression than the clinical and routine laboratory indicators described above. We hypothesise these biomarkers (particularly sFlt1 and soluble endoglin) will be significantly lower among the group given esomeprazole.

7.5.2 Urine samples

Urine samples will be collected 2 times per week and sent for spot protein: creatinine ratios. 24-hour protein excretion is routinely measured only once on admission. For the purposes of this study we will repeat it weekly. This will be performed at the Tygerberg Laboratory.

7.5.3 Cord Blood Samples

Cord Blood Samples will be collected at delivery and will be labelled with the participant's trial number and folder number. These samples will also be stored and sent to the University of Melbourne for further analyses where they will be analysed in the Translational Obstetrics Laboratory. We plan to measure esomeprazole levels in the cord blood obtained at the time of the delivery.

7.5.4 Placental samples

Placental samples will be collected at delivery from women who have consented for this to be performed. We will take three 1cm^3 full thickness biopsies of the placenta. Each sample will be frozen and stored in -80 degree freezer within a PIE Trial storage box. A further sample will be collected and fixed in formalin.

We plan to measure the following in the placental samples:

- **Expression of heme-oxygenase-1 (both mRNA and protein levels)**
- **Expression of anti-angiogenic factors in the placentas**
- Perform a microarray to examine the **mRNA expression of key anti-oxidant and hypoxia pathways**.
- **Antiangiogenic factors associated with pre-eclampsia:** sFlt1 and soluble Endoglin
- **Immunohistochemistry**

In addition, we plan to store remaining samples to measure other relevant analytes that may yet be discovered in relation to pre-eclampsia. We will not perform any genetic testing on these samples. These tests will be done in the Translational Laboratory at Melbourne University.

7.6 Withdrawal from the study

All participants will be informed that they are free to withdraw from the study at any time, and that this will not affect their clinical care. In the event of a withdrawal, we will ask whether we can still collect clinical data and include them in our analyses.

8.0 Data management and statistical analysis

8.1 Data management

Data will be collected prospectively by the researchers and data checking and entry of the completed data collection forms will be reviewed. Duplicate copies of original data collection forms will be used for quality control purposes.

8.2 Data recording

Data will be collected on data capture sheets will be transcribed onto a Microsoft Excel spreadsheet. Only the participant number will be entered onto the spreadsheets. Data cleaning will be performed on an ongoing basis and again at the end of the study.

8.3 Handling of missing data

If data is missing the original data extraction sheets will be reviewed and if needed the original patient notes will be reviewed.

8.4 Data processing

Data entry and checking will be continuous, and queries will be followed vigorously to ensure clarification without delay.

8.5 Analysis plan

The analyses will be on an intention-to-treat principle with comparisons made between proton pump inhibitors and placebo, for primary and secondary outcomes. Comparisons will be expressed as relative risks or mean differences with 95% confidence intervals.

8.6 Statistical methods

The patient characteristics, by treatment group, will be presented as mean (SD), median [25th – 75th percentile], minimum, maximum and count (%) depending upon type and distribution. Significance level is set at 0.05 and all hypothesis testing will be two-sided.

The primary outcome will not be adjusted for multiple comparisons but the secondary outcomes will be adjusted for multiple comparisons using a small number of pre-specified outcomes.

Primary outcome

We plan to perform two analyses: 1) primary intention to treat analysis (ITT) and 2) a treatment received (TR) analysis to examine response among those who actually took the tablets. The primary outcome (prolongation in days) between treatment groups will be tested using ANCOVA regression analysis with both treatment group and gestational strata as covariates.

We will present results as mean group difference with 95% confidence intervals (95%CI). Standard regression diagnostics will be performed and transformation of primary outcome, to achieve adequate distributions of residuals, if indicated. We will also present survival analyses (ie time until delivery), using Cox proportional hazards regression and Kaplan-Meier survivorship curves.

Secondary Outcomes

For these composite outcomes or single outcomes, continuous variables will be compared using either T-test (for normally distributed variables) or Mann-Whitney U (non-normally distributed). Categorical values will be compared using chi-squared test. For the longitudinal data of plasma sFlt-1, sEng and endothelin 1 levels, we will 1) graph the data longitudinally 2) compare levels between the groups relative to gestational age 3) compare levels between groups relative to days after recruitment and 4) compare levels between groups at delivery.

The various maternal and fetal outcomes will be compared as either composite outcomes or as single variables, listed as per 6.2. Continuous variables will be compared using either T-test (for normally distributed variables) or Mann-Whitney U (non-normally distributed). Categorical values will be compared using chi-squared test.

The same approach will be used to compare circulating sFlt-1, sEng or other molecules/variables measured subsequently in the laboratory.

9.0 Safety and Monitoring procedures

9.1 Adverse event

All Adverse events will be documented and reported. An adverse event includes

- Any unintentional, unfavourable clinical signs or symptoms. This includes complications of pre-eclampsia.
- Any new illness or disease or the deterioration of existing disease or illness.
- Any clinically relevant deterioration in any laboratory or clinical tests.

These events will be recorded on the daily data capture sheets.

The following are not considered adverse effects:

- A pre-existing condition (unless it worsens significantly in pregnancy over and above what may be expected with the concurrent diagnosis of pre-eclampsia).
- Diagnostic or therapeutic procedures such as surgery.

9.2 Serious adverse event

Serious adverse events include any of the following

- Maternal or fetal death.
- Threat to the life of the mother or baby.
- Event that results in a longer post-natal hospital stay.
- Event that results in a persistent or significant disability in the mother.
- Congenital or birth defect in the baby that is detected in the post-natal period and was not detected on ultrasound.

9.3 Expected serious adverse events

Certain serious adverse events will be expected as we are treating women with early onset pre-eclampsia with premature fetuses. We will expect to have serious adverse events related to the diagnosis of pre-eclampsia which include severe hypertension, intracranial haemorrhage, renal failure, abnormal hepatic function, disseminated intravascular coagulopathy, eclampsia, left ventricular failure, pulmonary oedema and haemorrhage. Complications of prematurity that may

be expected include sepsis, necrotising enterocolitis, respiratory complications, seizures, hypoglycaemia and intra-ventricular haemorrhage.

All serious adverse events will be reported to the principal investigator (or other nominated clinician) as soon as they have been identified. Full details including the diagnosis (if possible), the duration, actions taken, treatment given, outcome, causality and whether the event is expected or unexpected will be reported. A serious adverse event document will be completed and this will be sent to the data monitoring committee as soon as physically possible. The report will be emailed to the committee.

If an event is considered potentially related to the trial medication (and not in keeping with pre-eclampsia) it will then be immediately reported to the data monitoring committee and the manufacturer. Reporting and handling of adverse events will be in accordance with the GCP guidelines[49]. These procedures have been used in previous multicentre trials and proven to be efficient and compliant with the GCP principles and data management[49].

9.4 Unblinding

The need for unblinding should be very uncommon as the trial intervention is rarely associated with severe side effects and it will not delay or prevent standard management of the patient. If, however, unblinding is needed for any reason the principal investigator will be informed and, if necessary, the treatment will be revealed. Sheets with lists of 50 randomisation codes each will be sealed in individual, signed, numbered envelopes. If unblinding is requested, the relevant envelope will be opened by a person not involved in the trial in the presence of two witnesses, the group allocation read, and the list re-sealed in an envelope and signed. The randomisation envelopes will be accessible at all times to the principle investigator who will be contactable by mobile telephone. The principal investigator will co-ordinate the above process.

9.5 Reasons to stop the trial

If for any reason, there is a need to stop the trial prematurely this decision will be taken by the Data and Safety Monitoring committee.

10. Duration of the project

It is anticipated that the study can be completed in approximately 4 years (2015 – 2018). The duration of the study has been approximated using data from the study by Hall et al., who studied expectant management of pre-eclampsia in the same group of patients in the same hospital. They averaged 56 patients per year and the cohort was obtained from 1992 to 1997. Since then deliveries at Tygerberg hospital have increased substantially. In the past year at Tygerberg Hospital it is estimated that 146 women were expectantly managed with early onset pre-eclampsia. If we were able to randomise half of these women we would be able to recruit 73 per year. We would then be able to recruit 120 women over a two to three year period, but have decided to plan for a four year period in case the numbers are less than expected.

The recruitment will begin as soon as we have approval from Human Research Ethics and the South African Medicines Control Council and Tygerberg Hospital. This study has been registered with NHREC (South African Human Research Ethics Committee) and PACTR (Pan African Clinical Trials Registry). We anticipate that this process will require six to nine months.

11. Project management

The trial coordination and management will be done by the principal investigator (PI Cluver) in South Africa. The trial management will include coordination and execution of the following activities which require administrative and clinical research input.

11.1 Quality control procedures

Before recruitment

A trial pilot run on recruitment, trial procedures, data collection and sample collection will be done before the study starts.

During recruitment

1. Data checking and entry of the completed data collection forms will be continuous. All data will be double entered from the trial data sheets, cleaned and queries checked immediately. Data sheets and all other documents will be stored for future reference, audits and queries in a secure location.
2. Double-blinding with identical-looking placebos will avoid any biases at entry to the trial and during the monitoring of women and assessment of outcomes, with respect to the main comparison.
3. Randomisation will occur after informed consent has been given. If a treatment pack is not used for whatever reason, it will be retained unopened with the woman's name on it. The woman will remain in the trial and all data collected and reported on an 'intention to treat' basis. The used and unused packs will be kept in the centres until completion of the trial and any quality assurance checks thought necessary.
4. Good Clinical Practice (GCP) procedures (WHO 1995) will be followed.
5. A random sample of unused packs will be tested for content to ascertain whether the content matches coding.

After recruitment

Data will be analysed and reported on an intention-to-treat basis. The draft analysis plan will be finalised before recruitment starts. The trial report will include requirements laid out in the CONSORT statement (Begg et al 1996).

Follow-up procedures

All participants will be followed from enrolment until their discharge from hospital after delivery and all data will be recorded.

11.2 Trial committee

Data Monitoring Committee

The Data Monitoring Committee will have meetings four times per year to discuss the progress of the trial. They will be supplied with reports of progress every three months. They will be notified as per the protocol of all serious adverse effects. If there are serious concerns they will arrange an emergency meeting and they will be able to stop the trial at any time. Minutes of their meetings will be sent to the chair of the PIE Steering Committee for documentation and auditing purposes.

11.3 Preparation for the trial

Coordination activities

- Investigator meeting before recruitment: standardisation of trial procedures; reception, handling and storing of trial materials; recruitment rate
- Discussion of logistics of treatment administration
- Establish communication procedures

- Designation of Data Monitoring Committee
- Organization of initial and final collaborators meetings

Trial materials

- Preparation of data collection forms and consent forms
- Preparation of trial manuals
- Preparation of the boxes for the treatment packs and their contents

Data processing and system preparation

- Randomisation of subjects
- System set-up for data entry and validation
- System set-up for production of monitoring reports

Statistical issues

- Preparation of dummy tables
- Definition of monitoring reports to be produced

11.4 Conduct of the trial

Coordination activities

- Monitor trial progress
- Communication with the data monitoring committee

Data management and statistical analysis

- Data entry
- Data validation and production of queries
- Update of the master file using batches of new data or corrections coming from validation checks and/or answers to queries

- Monitoring reports: recruitment, adverse events, losses to follow-up, completeness of data for main outcomes

Administrative

- Assistance with the organization of trial-related meetings including travel arrangements
- Maintaining a mailing list of trial contacts (collaborators and data monitoring committee members)
- Posting, photocopying, faxing

12. Ethical aspects

12.1 Confidentiality

Participant confidentiality will be maintained throughout the course of the study. Only on-site study staff will have access to the data. In order to protect participant confidentiality, each participant will be assigned a unique Participant Identification number (Participant ID). Patient confidentiality will be protected according to the regulations set forth by Stellenbosch University's Human Research Ethics Committee or Institutional Review Board (IRB). Biological samples that are collected will only be identified with the folder number and participant's trial number. Laboratory staff will not have access to the personal data.

All personal data on paper format will be stored in a secure location and will be treated as strictly confidential. No data that could identify a participant will be released.

All data collected will be stored for a minimum of 5 years or longer as defined by the requirements of the Ethics Committee once the trial is completed.

12.2 Compensation for participation

There will be no compensation for participation in this trial and treatment will be no different to standard care.

13. Potential risks and benefits of the study

This study aims to find a treatment for early onset pre-eclampsia. If a treatment is found it could decrease both maternal and neonatal morbidity and mortality rates. If the drug was able to prolong gestation for women suffering from early onset pre-eclampsia it would enable them to deliver a healthier baby and would decrease the work load considerably for the neonatal services.

Proton pump inhibitors have been used in pregnancy and the chance of maternal or fetal effects is likely to be very small.

14. Resources and strengths of the study

14.1 Strengths of our study

1) Incidence of early onset pre-eclampsia is extremely high in South Africa: For reasons that are unknown the rates of early onset pre-eclampsia (and eclampsia) are higher in the developing world. Duley, for instance, reported the incidence of eclampsia in the developed world is 2-3/10,000, but 16-69/10,000 in the developing world (ie 8-30 fold increase)[50]. Audit data on the number of cases of early onset pre-eclampsia managed at Tygerberg Hospital suggests that this trial can be feasibly performed in just one hospital. In stark contrast with the incidence of early onset, pre-eclampsia in the developed world being ≤1%, a number of recruiting sites would be needed in first world countries. As an example the STAMP trial (assessing the treatment of early onset pre-eclampsia with pravastatin) aims to recruit 120 women in the UK. They have over 15 recruiting sites. Currently the two external supervisors (Prof Stephen Tong and Prof Susan Walker) are running a pilot trial in Australia on the use of pravastatin for the treatment of early onset pre-eclampsia. Pravastatin is a category D/X drug. In South Africa we will be using a class C drug.

2) Running the trial at Tygerberg Hospital will make the findings relevant globally: Tygerberg Hospital has many modern state of the art facilitates on par with tertiary referral hospitals in the developed world. We have a neonatal special care unit, a maternal high dependency unit and an academic centre that actively contributes to the global scientific literature. Thus, running this study here has the dual advantages of: 1) having large numbers of early onset pre-eclampsia seen only in the developing world and 2) a centre that practises modern obstetrics similar to that in the developed world.

3) It capitalises on a unique collaborative opportunity between Australia and South Africa: Dr Catherine Cluver is an academic clinician based at Tygerberg, South Africa. In 2013, she was the visiting maternal-fetal medicine Fellow at Mercy Hospital (where Prof Walker and Prof Stephen Tong are based). A close clinical and academic collaboration developed among the CIs who have worked together to generate this trial protocol.

14.2 Limitations of this study:

This study is powered to identify a prolongation of pregnancy of five days, and is underpowered to detect benefits such as a shorter (but still beneficial) prolongation of pregnancy. It is not powered to determine differences in significant maternal outcomes or neonatal benefits.

If esomeprazole does prove to be effective we would then proceed to a larger multicentre study which would be better powered to investigate these outcomes.

Furthermore, while this study may provide immense value in the developing world, it is possible any positive findings would need to be confirmed in the developed world before it is considered globally relevant.

15. Publication of results

We will publish the results of this trial (whether or not we prove our hypothesis) in publically accessible, peer reviewed journals. If we obtain a positive finding, it is possible the findings could be published in a high impact journal and could change clinical practice.

16. Appendices

Consent form
Patient information sheet
Trial schema flow chart
Budget

17. References

1. ACOG Committee on Obstetric Practice. Practice bulletin# 33: Diagnosis and management of preeclampsia and eclampsia. Obstetrics & Gynecology. 2002;99(1):159-167.

2. Dolea C, AbouZahr C. Global burden of hypertensive disorders of pregnancy in the year 2000. Evidence and information for policy (EIP). Geneva: World Health Organization. 2003.

3. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annual Review of Pathological Mechanical Disease. 2010;5:173-192.

4. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA: the journal of the American Medical Association. 2002;287(24):3183-3186.

5. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005;308(5728):1592-1594.

6. National Committee for Confidential Enquiries in Maternal Deaths. Mothers 2008–2010 fifth report on confidential enquiries into maternal deaths in South Africa. Compiled by the National Committee for Confidential Enquiry into Maternal Deaths. Department of Health, Republic of South Africa. 2012.

7. American College of Obstetricians and Gynaecologists' Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Obstetrics & Gynecology. 2013;122:1122.

8. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. The Lancet. 2005;365(9461):785-799.

9. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstetrics & Gynecology. 2003;102(1):181-192.

10. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. Hypertension in pregnancy. 2003;22(2):203-212.

11. Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proceedings of the Society for Experiemental Biology and Medicine. 1999;222(3):222-235.

12. Hung T, Burton GJ. Hypoxia and reoxygenation: A possible mechanism for placental oxidative stress in preeclampsia. Taiwanese Journal of Obstetrics and Gynecology. 2006;45(3):189-200.
13. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. New England Journal of Medicine. 2004;350(7):672-683.

14. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. New England Journal of Medicine. 2006;355(10):992-1005.

15. Roberts J, Redman C. Pre-eclampsia: More than pregnancy-induced hypertension. The Lancet. 1993;341(8858):1447-1451.

16. Gozzelino R, Jeney V, Soares MP. Mechanisms of cell protection by heme oxygenase-1. Annual Review of Pharmacology and Toxicology. 2010;50:323-354.

17. Levytska K, Baczyk D, Drewlo S. Heme oxygenase-1 in placental development and pathology. Placenta. 2013.

18. Ahmed A, Rahman M, Zhang X, et al. Induction of placental heme oxygenase-1 is protective against TNFalpha-induced cytotoxicity and promotes vessel relaxation. Molecular Medicine. 2000;6(5):391-409.

19. Cudmore M, Ahmad S, Al-Ani B, et al. Negative regulation of soluble flt-1 and soluble endoglin release by heme oxygenase-1. Circulation. 2007;115(13):1789-1797.

20. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011;123(24):2856-2869.

21. Ramma W, Ahmed A. Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia. Journal of Reproductive Immunology. 2014.

22. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. . 2011;31(1):33-46.

23. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. Journal of Clinical Investigation. 2003;111(5):649-658.

24. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nature Medicine. 2006;12(6):642-649.

25. Costantine MM, Tamayo E, Lu F, et al. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced preeclampsia. Obstetrics and Gynecology. 2010;116(1):114-120.

26. Fox KA, Longo M, Tamayo E, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble fms-like tyrosine kinase-1–induced preeclampsia. Obstetrics and Gynecology. 2011;205(4):366. e1-366. e5.

27. Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. Proceedings of the National Acadamy of Sciences U S A. 2011;108(4):1451-1455.

28. Brodsky SV, Goligorsky MS. Endothelium under stress: Local and systemic messages. 2012;32(2):192-198.

29. Aggarwal P, Chandel N, Jain V, Jha V. The relationship between circulating endothelin-1, soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia. Journal of Human Hypertension. 2012;26(4):236-241.

30. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: A meta-analysis. American Journal of Gastroenterology. 2009;104(6):1541-1545.

31. Shimazu H, Matsuoka T, Ishikawa Y, Imanishi M, Fujii T. Reproductive and developmental toxicity study of omeprazole sodium in rats. Oyo Yakuri-Pharmacometrics. 1995;49(5):573-592.

32. Richter J. Review article: The management of heartburn in pregnancy. Alimentary Pharmacological Therapy. 2005;22(9):749-757.

33. Teratology Society Public Affairs Committee. FDA classification of drugs for teratogenic risk. Teratology. 1994;49(6):446-447.

34. Rhim AD, Hardy JR, Haynes K, Testani JM, Yang Y. Maternal use of proton pump inhibitors (PPI) during pregnancy is associated with an increased risk for cardiac birth defects: Analysis of 208,951 pregnancies from the GPRD/THIN database. Gastroenterology. 2010;138(5):S-63.

35. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. New England Journal of Medicine. 2010;363(22):2114-2123.

36. Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Digestive Diseases and Sciences. 2012;57(3):699-705.

37. Hall D, Odendaal H, Steyn D, Grove D. Expectant management of early onset, severe pre-eclampsia: Maternal outcome. BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(10):1252-1257.

38. Ryan TP. Methods of determining sample sizes. Sample Size Determination and Power. 2013:17 November 2013.

39. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2014;4(2):105-145.

40. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Obstetrics and Gynecology. 1988;158(4):892-898.

41. Mattar F, Sibai BM. Eclampsia VIII: Risk factors for maternal morbidity. Obstetrics and Gynecology. 2000;182(2):307-312.

42. World Health Organization. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Tech Rep Ser. 1995;850:97-137.

43. Duley L. The global impact of pre-eclampsia and eclampsia. Seminars in Perinatology. 2009;33(3):130-137.

2. PIE trial patient information leaflet

PATIENT INFORMATION LEAFLET: PIE TRIAL

SUMMARY

Name of principal investigator: Dr Cathy Cluver

Name of research midwife: ……..

Contact number: ……

Website: …….

What is pre-eclampsia?
Pre-eclampsia is a serious condition that is only found in pregnancy.
It is associated with high blood pressure and can affect different parts of your body like the kidneys.
At present there is no effective treatment for pre-eclampsia except for birth of your baby but premature birth may cause medical problems for the baby.
For this reason we will keep you in hospital to monitor your pregnancy and health so that we can try and safely prolong your pregnancy to prevent your baby from possibly suffering some of the complications of a premature birth. This is the normal care that all women with early pre-eclampsia have.

The trial:
You are being invited to participate in a clinical trial that may help with finding a treatment for pre-eclampsia. This trial is to determine whether esomeprazole (a medication that is commonly used for reflux) can treat pre-eclampsia. This treatment may or may not improve your condition and may or may not delay the need for your baby to be born prematurely. This medication is safe in pregnancy and has been used by many pregnant patients.

If you decide to take part in the trial you may be given esomeprazole tablets or you may be given a placebo (dummy) tablet. You, the doctors and the nurses will not know what treatment you are being given. There is a 1 in 2 chance that you will be given the placebo or the esomeprazole tablet. Both tablets will look identical. Everyone in the study will receive exactly the same treatment as patients that are not in the study. If you are involved in the study you may have extra ultrasounds and we may need to collect extra blood from you while pregnant and at delivery a sample of blood from the cord and part of the placenta when you deliver.

If you would like to be involved in the clinical trial it will be important to start the medication as soon as possible. If you have any further questions about the study you can ask us questions at any time and we can be contacted on the telephone numbers given above.

BACKGROUND INFORMATION ON PRE-ECLAMPSIA

What is pre-eclampsia?

Pre-eclampsia is a serious medical condition that affects only pregnant women. It is caused by products released from the placenta that cause the mother to then suffer from high blood pressure. It commonly also effects the kidneys and this is seen by measuring the amount of protein in the urine. Pre-eclampsia can affect other organs in the body and can cause liver problems, blood clotting problems, and in severe cases seizures and stroke.

How do we treat pre-eclampsia?

At present there is no known treatment for this condition apart from delivery of the baby and the placenta. Early delivery can be associated with medical problems for the baby. Babies that are born too early can suffer from breathing problems, problems with their intestines and can have bleeding in the brain. We know that every day in early pregnancy can make a difference to the babies' survival and for this reason we admit pregnant mothers with this condition early in pregnancy to the hospital. Many studies have shown that this is a safe form of management as long as mothers are monitored very closely in the hospital.

When will I have my baby?

When you reach 34 weeks we will consider delivering the baby as we know that most babies born at this age do well. If you develop any complications or if the baby is in distress we will deliver your baby before we reach 34 weeks.

What treatment will I receive?

During your stay in hospital we will be monitoring your blood pressure. We will be checking your urine everyday to see how much protein you are losing through the kidneys. Twice a week we will be doing blood tests to monitor for complications. A doctor will be seeing you every day to check you and your baby's health. Every week there will be a large number of doctors that come and do a ward round to make sure that you and your baby are well. Your baby will be monitored 4 times a day with a monitor on your tummy. Ultrasound examinations of your baby will be performed.

You will receive treatment to control your blood pressure if it is needed and we may prescribe some pregnancy vitamins and supplementations. If you loose a large amount of protein in your urine you may be started on a treatment to prevent blood clots.

INVITATION TO BE INVOLVED IN THE PIE TRIAL

You are being invited to participate in a research project to find out whether a drug called esomeprazole can be used to treat pre-eclampsia. The name of the study is the Pre-eclampsia Intervention with Esomeprazole (PIE) trial. It is important that you read all the information provided about the trial before you decide to take part and that you understand why we are doing the research and what you would need to do if you were involved in the study. If you have any questions about the trial you can ask your doctor, the midwives or any of the staff from the research project. You can talk to any of the other women who have decided to be involved or not involved in the study.

Why are we doing this study?

Pre-eclampsia is a dangerous condition in pregnancy. If we could find a treatment for pre-eclampsia we would possibly be able to save many pregnant mothers and babies. There is no known treatment for pre-eclampsia. Other researchers in England are doing studies with a drug called pravastatin but have not finished their study yet.

What is the purpose of this study?

Recent research has shown that there are substances produced by the placenta that can cause pre-eclampsia. Work done in a laboratory in Melbourne, Australia has shown that these substances may be reduced by the group of drugs called proton pump inhibitors. Esomeprazole is one of these drugs. The PIE trial is the first trial in the world that will look to see if esomeprazole can be used to treat pre-eclampsia.

Why have I been invited to be involved in this study?

You have been invited to be in this study as you have been diagnosed with pre-eclampsia. We would like to include 120 women with pre-eclampsia in this study.

Do I have to be in the study?

It is voluntary to be in the study and it is your choice to be involved or to not be involved. Your treatment will not be any different if you are not involved in the study. You can decide at any stage in the pregnancy to withdraw from the study and you will not have to give a reason for why you want to withdraw.

Will I need to do anything extra if I am in the study?

Once you have decided to be in the trial you will need to sign an informed consent document. This form will say that you want to be involved in the study and that you have read and understood the information we have given you about the trial.

You will then need to take one extra tablet in the evening before you go to bed until the baby is delivered. One of the research team will visit you every day to see how you are feeling and to collect information about your pregnancy. When your routine blood tests are done we will take an extra sample of blood for the study. On the first day that you take the medication we will need to take an extra sample of blood. We may need to do extra ultrasound examinations of your baby. Once your baby is born and the cord has been cut we will take a small amount of blood from the placenta. We will take a small sample from the placenta which will be sent for testing. We will follow you up after the delivery of the baby. The samples taken may be sent overseas for further testing to try to find a treatment for pre-eclampsia. Only tests related to finding a cure for pre-eclampsia will be performed on the samples taken.

Is esomeprazole treatment safe in pregnancy?

Esomeprazole is used in pregnancy to treat reflux and gastric ulcers. There have been no reports of fetal problems in humans or complications in human pregnancies caused by this medication or other medications in the same class of drug.

Are there any side effects of esomeprazole?

All drugs may have side effects. Side effects that have been associated with the use of esomeprazole include headache, diarrhea, abdominal pain, constipation and a dry mouth. There are certain drugs that cannot be used with esomeprazole. If you are taking one of these drugs you will not be asked to participate in the trial. We will provide you with a copy of the product information leaflet if you would like more information.

Will I receive the placebo treatment or the esomeprazole treatment?

We will not know until the study is completed whether you were taking the dummy/placebo tablet or the esomeprazole tablet. The tablets will look identical and the midwives, nurses and doctors will not know which tablet you are taking. The tablet packages will be the same and only the pharmacy organizing the tablets will know what is in each packet. Once the study is completed we will then find out what tablets you were taking.

What will happen to the blood samples and the samples taken from the placenta?

These samples will be stored and may be sent to a laboratory at Melbourne University, Australia. The laboratory staff may do tests to see if esomeprazole can be used to treat pre-eclampsia. Only tests related to pre-eclampsia will be done on the samples. Your samples will not be used for genetic testing.

Will my information be kept confidential?

All information collected in the study will be kept strictly confidential. Information collected will only be available to people directly involved in the study. Your information will be given a study number and your name will not be used for identifying any of your samples. The data collected will be locked in a secure location and only people involved in the study will have access to this information. Your name will not appear on any presentations or publications relating to this study. Only your study number will be on the samples taken and none of the laboratory staff will have access to your name or contact details.

Are there any benefits of me for being involved with this study?

Only half of the women in this trial will be given esomeprazole. If you do receive this treatment you may or may not benefit from the effects of this drug and you may or may not have improvement in your pre-eclampsia. There are no other direct benefits for you being involved in this study. By being involved you may help us find a treatment for pre-eclampsia which could help many pregnant mothers in your situation in the future.

What are the disadvantages of being in the study?

You will need to take an extra tablet in the evenings and we may need to take a few extra samples of your blood for testing.

What will happen if there is any new information while I am involved in the study?

There will be an independent committee that will be reviewing the results of the trial on an ongoing basis. If there is any new information you will be informed about it and will then be able to decide if you would like to continue with the trial

What will happen with the results of this research project?

The results of this study will be published in medical journals and will be presented at medical conferences. Your private details will not be included in the articles or presentations

Who has developed this study and who has reviewed the study?

This study has been developed by a team of researchers from Melbourne University in Australia and Stellenbosch University, South Africa. We have had experts in the field of pre-eclampsia involved with the study. This study has been approved by the Research Ethics Committee at the University of Stellenbosch and by the South African Medical Research Council.

Who has paid for this study?

This study has been funded by grants from the Medical Research Foundation for Mothers and Babies, and University of Melbourne.

Who do I contact if I have a problem?

If you have any concerns or problems you will be able to speak to the researchers involved in the study at anytime. If you have a more serious concern there is a safety and adverse event committee that you will be able to contact.

This study has been approved by the **Health Research Ethics Committee (HREC) at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

You can contact Dr Cathy Cluver at telephone number 082 321 0298 if you have any further queries or encounter any problems.

You can contact the **Health Research Ethics Committee** at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided above). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 9201
e-mail: mogobm@health.gov.za

What do I do if I do not want to continue with the study?

If you decide to not continue with the trial at any stage you may withdraw and it will not affect the care that you are receiving in any way. You will not be asked to give us a reason for why you want to withdraw from the study. We will ask you if it will be possible to collect information

about your pregnancy and delivery and we will ask you if it is possible for us to use the samples that we have already collected.

Who do I speak to if I have questions about the study?

If you have any questions you can discuss these with the research team, your doctor, the midwives involved in your care or with any of the other participants in the trial.

Thank you for taking the time to read this information leaflet about the PIE trial.

We hope that you will consider being involved in our study.

Please keep this copy of the information leaflet. If you do decide to be involved in the study you will be given a copy of the consent form

3. PIE trial consent form

The Pre-eclampsia Intervention with Esomeprazole (PIE) trial:
a double blind randomised, placebo-controlled trial to treat early onset severe preeclampsia

INFORMED CONSENT FORM

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Dr Catherine Anne Cluver

RESEARCH MIDWIFE: Name: ……
Contact number: ……
Email: …….

ADDRESS: Department of Obstetrics and Gynaecology
Tygerberg Hospital and University of Stellenbosch

You are being invited to take part in a research project. Please take some time to read the patient information leaflet given to you which will explain the details of this project.

Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. You will be given as much time as you need to decide whether you would like to be involved in the study. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee (HREC) at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

You can contact Dr Cathy Cluver at telephone number 082 321 0298 if you have any further queries or encounter any problems.

You can contact the **Health Research Ethics Committee** at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I …….. agree to take part in a research study entitled: The Pre-eclampsia Intervention with Esomeprazole (PIE) trial: a double blind randomised, placebo-controlled trial to treat early onset preeclampsia.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ……. on (*date*) ……..

…….. ……..

Signature of participant **Signature of witness**

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged her to ask questions and took adequate time to answer them.
- I am satisfied that she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) ..... on (*date*) ……..

....

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) ……..

  using the language medium of Afrikaans/Xhosa.

- We encouraged her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) ……..

....

Signature of interpreter **Signature of witness**

4. PIE trial published correspondence

Accepted Manuscript

Esomeprazole to treat women with preeclampsia: possible implications in the nitric oxide homeostasis

Valeria C. Sandrim, PhD, Mayara Caldeira-Dias, MSc, Marcelo F. Montenegro, PharmD, PhD

PII: S0002-9378(18)30877-9

DOI: 10.1016/j.ajog.2018.10.008

Reference: YMOB 12372

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 22 August 2018

Accepted Date: 2 October 2018

Please cite this article as: Sandrim VC, Caldeira-Dias M, Montenegro MF, Esomeprazole to treat women with preeclampsia: possible implications in the nitric oxide homeostasis, *American Journal of Obstetrics and Gynecology* (2018), doi: https://doi.org/10.1016/j.ajog.2018.10.008.

Esomeprazole to treat women with preeclampsia: possible implications in the nitric oxide homeostasis

Valeria C. Sandrim[1,*], PhD, Mayara Caldeira-Dias,MSc[1], and Marcelo F Montenegro[2,*], PharmD, PhD

From [1]Institute of Biosciences of Botucatu, Universidade Estadual Paulista (UNESP) and [2]Department of Physiology & Pharmacology, Karolinska Institute, Stockholm, Sweden

Address requests for reprints to corresponding author:

Marcelo F. Montenegro, PharmD, PhD
Department of Physiology & Pharmacology
Karolinska Institutet
Biomedicum Q5B, Solnavägen 9, 171 77 Stockholm, Sweden
Phone Mobile: +46 76 237 10 44
Email: marcelo.montenegro@ki.se

OR

Valeria C. Sandrim, PhD
Universidade Estadual Paulista (UNESP)
Department of Pharmacology, Institute of Biosciences of Botucatu
Distrito de Rubião Junior S/N 18618-000 Botucatu, SP, Brazil
Phone: +55 14 3880 0228
Email: valeria.sandrim@unesp.br

Total word count: 394

Conflicts of Interest: The authors report no conflict of interest.

Dear Editor: We read with interest the paper by Cluver et al. evaluating the use of proton pump inhibitor (PPI) esomeprazole to treat women with preterm preeclampsia.[1] While the 40mg of daily oral esomeprazole tested in their study did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating sFlt-1 concentrations, the authors discuss that this dosage of esomeprazole may be too low to treat preterm preeclampsia and suggest that higher doses may still be effective.[1] We would like to bring up that the use of PPIs has been associated to increased risk of adverse cardiovascular events,[2,3] possibly due interferences in nitric oxide (NO) homeostasis. Several studies support a decreasing in NO in preeclampsia, and importantly preeclampsia induces subclinical hemolysis which results in NO scavenging.[4] PPIs also reduce endogenous formation of NO through inhibition of the enzyme dimethylarginine dimethylaminohydrolase (DDAH), which degrades asymmetric diemethylarginine (ADMA), an endogenous nitric oxide synthase (NOS) inhibitor and which is increased in preeclampsia compared with healthy pregnant.[2] In addition, we recently demonstrated that esomeprazole blocks the blood pressure-lowering effects of nitrite, preventing thus possible beneficial properties from dietary nitrate.[3] While is most widely known that the classical NO formation is mediated by NO synthases from L-arginine, an alternative pathway for NO generation named nitrate-nitrite-NO has been described, in which the oxidation products of NO metabolism nitrite (NO_2^-) and nitrate (NO_3^-) are recycled back to NO in blood and tissues.[5] Nitrate is commonly found in our everyday diet and its ingestion exerts robust NO-like effects, including reduction in blood pressure and improvements in vascular function.[5] These beneficial cardiovascular effects of dietary nitrate involve an entero-salivary circulation in which nitrate is absorbed manly in the gastrointestinal tract and then actively taken up and concentrated in salivary glands, resulting in high nitrate levels in saliva.[5] Commensal bacteria in the mouth then reduce salivary nitrate to nitrite and when saliva enters the acidic stomach, nitrite is rapidly protonated to form nitrous acid (HNO_2), which decomposes further to form NO affecting blood pressure.[3] The use of PPIs increases gastric pH and this contributes to impairments of the nitrate-nitrite-NO pathway described above. In summary,

PPIs may alter NO homeostasis by inhibition of DDAH and preventing NO generation from dietary nitrate-nitrite. We believe these recently discovered properties of PPIs should be account in further studies using PPIs, especially in patients in cardiovascular risk.

Disclosures

none

References

1 Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomised placebo controlled trial. Am J Obstet Gynecol 2018; S0002-9378(18)30606-9.

2 Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013; 128: 845-53.

3 Montenegro MF, Sundqvist ML, Larsen FJ, et al. Blood Pressure-Lowering Effect of Orally Ingested Nitrite Is Abolished by a Proton Pump Inhibitor. Hypertension 2017; 69: 23-31.

4 Sandrim VC, Montenegro MF, Palei AC, et al. Increased circulating cell-free hemoglobin levels reduce nitric oxide bioavailability in preeclampsia. Free Radic Biol Med 2010; 49: 493-500.

5 Lundberg JO, Carlström M, Weitzberg E. Metabolic Effects of Dietary Nitrate in Health and Disease. Cell Metab 2018; 28: 9-22.

Accepted Manuscript

Reply to L18-102AR1 Sandrim et al

Catherine Cluver, Natalie Hannan, Stephen Tong

PII: S0002-9378(18)30878-0

DOI: 10.1016/j.ajog.2018.10.009

Reference: YMOB 12373

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 20 September 2018

Accepted Date: 2 October 2018

Please cite this article as: Cluver C, Hannan N, Tong S, Reply to L18-102AR1 Sandrim et al, *American Journal of Obstetrics and Gynecology* (2018), doi: https://doi.org/10.1016/j.ajog.2018.10.009.

TITLE PAGE:

Title:

Reply to L18-102AR1 Sandrim et al

Authors and affiliations:

Catherine Cluver[1,2,3], Natalie Hannan[1,2], Stephen Tong[1,2]

[1]Mercy Perinatal, Mercy Hospital for Women, Heidelberg 3084, Victoria, Australia

[2]Translational Obstetrics Group, University of Melbourne, Victoria, Australia

[3]Department of Obstetrics and Gynaecology, Stellenbosch University

Corresponding Author

Dr Catherine Cluver

Department of Obstetrics and Gynaecology, Stellenbosch University

Francie van Zyl Drive

Tygerberg

7505

Email: cathycluver@hotmail.com

Phone: +27823210298

Total word count: 399

Conflicts of interest: The authors report no conflicts of interest.

Text:

Sandrim et al advises caution in evaluating proton pump inhibitors (PPI) to treat preeclampsia, in light of their prior work suggesting they may have actions that could increase blood pressure, by interfering with nitric oxide (NO) homeostasis.

We agree that treatment trials should include interim analyses to examine the possibility of risk. However, we resolutely disagree the work they cite provides a sufficient weight of evidence to suggest PPIs should not be further investigated for their potential to treat preeclampsia, *for the following reasons*:

1) While our treatment trial did not show benefit, there was no evidence that those exposed to PPIs had an increased incidence of higher/worsening blood pressures.

2) In our preclinical laboratory work[1], we show PPIs may have multiple actions to mitigate the vascular damage caused by preeclampsia, well beyond the singular pathway of the NO. They include: Decreasing placental and endothelial secretion of soluble fms-like tyrosine kinase-1 (sFlt1), soluble endoglin (sEng), endothelial 1 (ET-1) and pro-inflammatory cytokine secretion (These cause increased blood pressure and vascular dysfunction in preeclampsia), mitigate endothelial dysfunction in multiple assays, induce vasodilation in whole human omental vessels, and importantly, reduced blood pressure in an animal model of preeclampsia.

3) Ghebremariam et al [2] showed omeprazole decreased expression of nitric oxide synthase (enzyme that produces NO). In contrast, we found esomeprazole significantly increased eNOS expression. Hence, we could not validate a key finding of their work.

4) Their statement that PPIs are associated with an increased risk of adverse cardiovascular events refers to literature on older persons with chronic morbidities taking PPIs indefinitely. This is a very different vascular profile to pregnant women, even those with preeclampsia.

5) Supporting our preclinical findings, Selah et al [3] independently reported that the concurrent use of PPIs among a cohort of pregnant women with suspected hypertensive disorder of pregnancy at the time of enrolment was associated with lower circulating

sFlt/sEng/ET1, no increase in blood pressure, less gestational hypertension, longer interval to delivery and a higher birthweight. It was in a pregnant population and identified potential benefits and certainly no tendency towards increased blood pressure.

A RCOG report in 2015 highlights the dire state of therapeutic development in pregnancy research. Patient safely is resolute but an overly cautious approach in considering any potential treatments may mean that we will never make an impact on obstetric complications that claims the lives of thousands of women and babies.

References:

1. Onda K, Tong S, Beard S, et al. Proton Pump Inhibitors Decrease Soluble fms-Like Tyrosine Kinase-1 and Soluble Endoglin Secretion, Decrease Hypertension, and Rescue Endothelial Dysfunction. Hypertension 2017; 69(3): 457-68.

2. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013; 128(8): 845-53.

3. Saleh L, Samantar R, Garrelds IM, van den Meiracker AH, Visser W, Danser AHJ. Low Soluble Fms-Like Tyrosine Kinase-1, Endoglin, and Endothelin-1 Levels in Women With Confirmed or Suspected Preeclampsia Using Proton Pump Inhibitors. Hypertension 2017; 70(3): 594-600.

5. Cochrane review

Cochrane Database of Systematic Reviews

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term (Review)

Cluver C, Novikova N, Koopmans CM, West HM

Cluver C, Novikova N, Koopmans CM, West HM.
Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD009273.
DOI: 10.1002/14651858.CD009273.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Catherine Cluver[1], Natalia Novikova[2], Corine M Koopmans[3], Helen M West[4]

[1]Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, Tygerberg, South Africa. [2]Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa. [3]Department of Obstetrics and Gynecology, University Medical Centre Groningen, Groningen, Netherlands. [4]Institute of Psychology, Health and Society, The University of Liverpool, Liverpool, UK

Contact address: Catherine Cluver, Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Hospital, PO Box 19063, Tygerberg, Western Cape, 7505, South Africa. cathycluver@hotmail.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 1, 2017.

Citation: Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD009273. DOI: 10.1002/14651858.CD009273.pub2.

ABSTRACT

Background

Hypertensive disorders in pregnancy are significant contributors to maternal and perinatal morbidity and mortality. These disorders include well-controlled chronic hypertension, gestational hypertension (pregnancy-induced hypertension) and mild pre-eclampsia. The definitive treatment for these disorders is planned early delivery and the alternative is to manage the pregnancy expectantly if severe uncontrolled hypertension is not present, with close maternal and fetal monitoring. There are benefits and risks associated with both, so it is important to establish the safest option.

Objectives

To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with hypertensive disorders, at or near term (from 34 weeks onwards).

Search methods

We searched Cochrane Pregnancy and Childbirth Trials Register (12 January 2016) and reference lists of retrieved studies.

Selection criteria

Randomised trials of a policy of planned early delivery (by induction of labour or by caesarean section) compared with a policy of delayed delivery ("expectant management") for women with hypertensive disorders from 34 weeks' gestation. Cluster-randomised trials would have been eligible for inclusion in this review, but we found none.

Studies using a quasi-randomised design are not eligible for inclusion in this review. Similarly, studies using a cross-over design are not eligible for inclusion, because they are not a suitable study design for investigating hypertensive disorders in pregnancy.

Data collection and analysis

Two review authors independently assessed eligibility and risks of bias. Two review authors independently extracted data. Data were checked for accuracy.

Main results

We included five studies (involving 1819 women) in this review.

There was a lower risk of **composite maternal mortality and severe morbidity** for women randomised to receive planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women (*evidence graded high)*). There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with lower risk of **HELLP syndrome** (RR 0.40, 95% CI 0.17 to 0.93, 1628 women; three studies) and **severe renal impairment** (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study).

There was not enough information to draw any conclusions about the effects on **composite infant mortality and severe morbidity**. We observed a high level of heterogeneity between the two studies in this analysis (two studies, 1459 infants, I^2 = 87%, Tau^2 = 0.98), so we did not pool data in meta-analysis. There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with higher levels of **respiratory distress syndrome** (RR 2.24, 95% CI 1.20 to 4.18, three studies, 1511 infants), and **NICU admission** (RR 1.65, 95% CI 1.13 to 2.40, four studies, 1585 infants).

There was no clear difference between groups for **caesarean section** (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, *evidence graded moderate)*, or in the **duration of hospital stay** for the mother after delivery of the baby (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15, two studies, 925 women, *evidence graded moderate)* or for the baby (MD -0.20 days, 95% CI -0.57 to 0.17, one study, 756 infants, *evidence graded moderate)*.

Two fairly large, well-designed trials with overall low risk of bias contributed the majority of the evidence. Other studies were at low or unclear risk of bias. No studies attempted to blind participants or clinicians to group allocation, potentially introducing bias as women and staff would have been aware of the intervention and this may have affected aspects of care and decision-making.

The level of evidence was graded high (composite maternal mortality and morbidity), moderate (caesarean section, duration of hospital stay after delivery for mother, and duration of hospital stay after delivery for baby) or low (composite infant mortality and morbidity). Where the evidence was downgraded, it was mostly because the confidence intervals were wide, crossing both the line of no effect and appreciable benefit or harm.

Authors' conclusions

For women suffering from hypertensive disorders of pregnancy after 34 weeks, planned early delivery is associated with less composite maternal morbidity and mortality. There is no clear difference in the composite outcome of infant mortality and severe morbidity; however, this is based on limited data (from two trials) assessing all hypertensive disorders as one group.

Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions. These studies should also include infant and maternal morbidity and mortality outcomes, caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby.

An individual patient meta-analysis on the data currently available would provide further information on the outcomes of the different types of hypertensive disease encountered in pregnancy.

PLAIN LANGUAGE SUMMARY

Is it safer to deliver a baby immediately or wait if the mother has high blood pressure after 34 weeks of pregnancy that is not persistently severe?

What is the issue?

Women who have high blood pressure (hypertension) during pregnancy or who develop pre-eclampsia (high blood pressure with protein in the urine or other organ systems involvement, or both) can develop serious complications. Potential complications for the mother are worsening of pre-eclampsia, development of seizures and eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), detachment of the placenta, liver failure, renal failure, and difficulty breathing because of fluid in the lungs.

Delivering the baby usually stops the mother's high blood pressure from getting worse, but a baby who is born prematurely may have other health problems, such as difficulty breathing, because the lungs are still immature. Induction of labour can lead to overstimulation of contractions and fetal distress. The alternative is waiting to deliver the baby while closely monitoring both the mother and her baby.

Why is this important?

As there are both benefits and risks to planned early delivery compared with waiting when the mother has high blood pressure toward the end of pregnancy, we wanted to know which is the safest option. We looked for clinical trials that compared planned early delivery, by induction of labour or by caesarean section, with a policy of delayed delivery of the baby.

What evidence did we find?

We searched for evidence on 12 January 2016 and found five randomised studies, involving 1819 women. Two of the studies were large, high-quality studies, in women with gestational hypertension, mild pre-eclampsia or deteriorating existing hypertension at 34 to 37 weeks (704 women) or with gestational hypertension or mild pre-eclampsia at 36 to 41 weeks (756 women). Fewer women who received planned early delivery experienced severe adverse outcomes (1459 women, *high-quality evidence*). There was not enough information to draw any conclusions about the effects on the number of babies born with poor health, with a high level of variability between the two studies (1459 infants, *low-quality evidence*). There was no clear difference between planned early delivery and delayed delivery for the number of caesarean sections (four studies, 1728 women, *moderate-quality evidence*), or the duration of the mother's hospital stay after the birth of the baby (two studies, 925 women, *moderate-quality evidence*) (or for the baby (one study, 756 infants, *moderate-quality evidence*)). More babies who were delivered early had breathing problems (respiratory distress syndrome, three studies, 1511 infants), or were admitted to the neonatal unit (four studies, 1585 infants). Fewer women who delivered early developed HELLP syndrome (three studies, 1628 women) or severe kidney problems (one study, 100 women).

Two studies compared women who had labour induced at 34 to 36 weeks and at 34 to 37 weeks with a comparison group who were monitored until 37 weeks, when induction was begun if labour had not started spontaneously. Three studies compared induction of labour at term or closer to term, at 37 completed weeks and at 36 to 41 weeks, with women who were monitored until 41 weeks when induction was begun if labour had not started spontaneously. Other inclusion and exclusion criteria also differed between the five studies.

No studies attempted to blind the women or their clinicians to which group they were in. Women and staff were aware of the intervention and this may have affected aspects of care and decision-making. Most of the evidence was of moderate quality, so we can be moderately certain about the findings.

What does this mean?

Overall, if a woman's baby was delivered immediately after 34 weeks, there was less risk of a complication for the mother and no clear difference in the overall rate of complications for the baby, but information was limited.

These findings are applicable to general obstetric practice when high blood pressure disorders during pregnancy are considered together. Further studies are needed to look at the different types of hypertensive disorders individually.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Planned early delivery versus expectant management for hypertensive disorders from 34 weeks' gestation to term

Patient or population: pregnant women with hypertensive disorders from 34 weeks' gestation to term
Setting: 2 studies in the Netherlands, 1 in India, and 1 in the USA
Intervention: planned early delivery
Comparison: expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GRADE				
Composite maternal mortality and morbidity	Study population		RR 0.69 (0.57 to 0.83)	1459 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	242 per 1000	167 per 1000 (138 to 201)				
	Moderate					
	235 per 1000	162 per 1000 (134 to 195)				
Composite infant mortality and morbidity			not pooled	1459 (2 RCTs)		This outcome was not pooled, due to substantial statistical heterogeneity (I^2 = 87%, Tau^2 = 0.98)
Caesarean section	Study population		RR 0.91 (0.78 to 1.07)	1728 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	267 per 1000	243 per 1000 (208 to 285)				
	Moderate					

	302 per 1000	275 per 1000 (236 to 324)			
Duration of hospital stay after delivery for mother (days)	The mean duration of hospital stay after delivery for mother (days) was 0	The mean duration of hospital stay after delivery for mother (days) in the intervention group was 0.16 fewer (0.46 fewer to 0.15 more)	-	925 (2 RCTs)	⊕⊕⊕○ MODERATE [1]
Duration of hospital stay after delivery for baby (days)	The mean duration of hospital stay after delivery for baby (days) was 0	The mean duration of hospital stay after delivery for baby (days) in the intervention group was 0.2 days fewer (0.57 fewer to 0.17 more)	-	756 (1 RCT)	⊕⊕⊕○ MODERATE [1]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Wide confidence interval crossing the line of no effect.

BACKGROUND

Description of the condition

Hypertensive disorders in pregnancy are significant contributors to maternal and perinatal morbidity and mortality in low-, middle- and high-income countries (Khan 2006). They occur in up to 10% of all pregnancies (Dolea 2003; Saftlas 1990; Steegers 2010) and in up to 11% of first pregnancies (Villar 2003). There is wide variation in the incidence between different countries, and regional differences may exist (Abalos 2013). This may be explained by differences in maternal age distribution, the proportion of primiparous women among the populations (Hutcheon 2011), and dietary differences such as low-calcium intake (Belizan 1980) and genetic characteristics.

There are a number of classification systems for the hypertensive disorders of pregnancy. The most recent classification system that has been published is from the International Society for the Study of Hypertensive Disorders in Pregnancy (ISSHP) (Magee 2014). Other commonly-used classification systems are the National Institute for Health and Clinical Excellence (NICE) classification system (NICE 2010), which is currently under review, and the American College of Obstetricians and Gynecologists classification of Hypertensive disorders in pregnancy (ACOG Hypertension in Pregnancy 2013).

The ISSHP classification

Hypertension in pregnancy: office or in-hospital systolic blood pressure (BP) greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Severe hypertension: systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.

Pre-existing (chronic) hypertension: hypertension that predates the pregnancy or appears before 20 weeks' gestation.

Gestational hypertension: hypertension that appears at or after 20 weeks of gestation.

Pre-eclampsia: gestational hypertension and new proteinuria or one or more adverse conditions or one or more serious complications (see Table 3 for definitions of adverse conditions and serious complications).

In this classification an adverse condition consists of maternal symptoms, signs, abnormal laboratory results and abnormal fetal monitoring that may herald the development of severe maternal or fetal complications and significant proteinuria is a value greater than or equal to 0.3 g/d in a complete 24-hour urine collection or a spot (random) urine sample with greater than or equal to 30 mg/mmol urinary creatinine.

Severe pre-eclampsia: pre-eclampsia associated with a severe complication that warrants delivery regardless of gestational age.

NICE classification

Pre-existing/chronic hypertension: hypertension defined as a systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg prior to pregnancy or hypertension presenting in the first 20 weeks of pregnancy, (on at least two occasions) or hypertension persisting until at least 12 weeks postpartum or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary (essential hypertension) or secondary (to various medical conditions) in aetiology.

Gestational hypertension: elevated blood pressure (systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg measured on two occasions at least four hours apart) in previously normotensive pregnant women presenting after 20 weeks of pregnancy without proteinuria.

Severe gestational hypertension: elevated systolic blood pressure of more than 160 mmHg and/or diastolic blood pressure of more than 110 mmHg at least four hours apart.

The diagnosis of gestational hypertension is temporary and becomes pre-eclampsia if proteinuria develops, or chronic hypertension if blood pressure is still elevated at 12 weeks postpartum, or transient hypertension of pregnancy if the blood pressure is normal at 12 weeks postpartum (Magloire 2012). About 15% to 25% of women with gestational hypertension will develop pre-eclampsia (Davis 2007). This may increase up to 46% the earlier the diagnosis of gestational hypertension is made (Barton 2001).

Pre-eclampsia: hypertension (systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg) measured on two occasions at least four hours apart presenting after 20 weeks with significant proteinuria (urinary protein: creatinine ratio greater than 30 mg/mmol or more than 0.3 g in a validated 24-hour urine specimen).

Severe pre-eclampsia: pre-eclampsia with severe hypertension (systolic blood pressure above 160 mmHg and/or diastolic blood pressure above 110 mmHg) or other signs/symptoms such as symptoms of central nervous system dysfunction, liver capsule distension, liver impairment, thrombocytopenia (decrease in the number of platelets), severe proteinuria of more than 3 g in 24 hours or 3+ on dipstick, renal impairment, oliguria (less than 500 mL in 24 hours), pulmonary oedema, intrauterine growth restriction or reduced liquor volume (Duley 2009).

Pre-eclampsia superimposed on pre-existing hypertension: new onset of proteinuria after 20 weeks of pregnancy in a woman with pre-existing hypertension. In cases where proteinuria is present in early pregnancy, pre-eclampsia is defined as worsening of hypertension or development of symptoms/signs of severe pre-eclampsia (August 2012).

Complications of hypertensive disorders during pregnancy are associated with worsening of pre-eclampsia, development of eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low

platelet count), placental abruption, liver failure, renal failure, pulmonary oedema, and maternal death (Sibai 2005).

ACOG Hypertension in Pregnancy Classification

Pre-eclampsia: Blood pressure greater than or equal to 140 mmHG systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure OR a blood pressure greater than or equal to 160 mmHg systolic or greater than or equal to 110 mm Hg diastolic, confirmed within a short interval to facilitate timely antihypertensive therapy with proteinuria, defined as greater than or equal to 300 mg per 24-hour urine collection or a protein/creatinine ratio greater than or equal to 0.3 mg/dL or a dipstick reading of 1+ if other quantitative methods are not available or in the absence of proteinuria, new onset hypertension with thrombocytopaenia, renal insufficiency, impaired liver function, pulmonary oedema or cerebral or visual symptoms.
Chronic hypertension: High blood pressure known to predate conception or detected before 20 weeks of gestation.
Chronic hypertension with superimposed pre-eclampsia: Include the following scenarios:
1. Women with hypertension only in early gestation who develop proteinuria after 20 weeks of gestation.
2. Women with hypertension and proteinuria before 20 weeks who develop a sudden exacerbation of hypertension, suddenly manifest other signs and symptoms such as an increase in liver enzymes, present with thrombocytopaenia, manifest with symptoms of right upper quadrant pain and severe headaches, develop pulmonary oedema or congestion, develop renal insufficiency or have sudden substantial sustained increases in protein excretion.
Gestational hypertension: New onset hypertension after 20 weeks gestation in the absence of accompanying proteinuria.

Description of the intervention

The definitive treatment of hypertensive disorders related to pregnancy is planned early delivery. The alternative is to manage the pregnancy expectantly with close maternal and fetal monitoring. The generic Cochrane protocols on interventions for preventing (Meher 2005) and treating (Duley 2009) pre-eclampsia and its consequences cite various Cochrane Reviews covering this subject. The World Health Organization (WHO) guidelines on prevention and treatment of pre-eclampsia and eclampsia provide a summary of available evidence on various interventions (WHO 2011). There are currently no data from randomised controlled trials on interventions to monitor women with hypertensive disorders of pregnancy.
The general approach on management involves frequent blood pressure measurement, frequent assessment of maternal symptoms (headache, blurred vision, epigastric or abdominal pain, vaginal bleeding, decrease in fetal movements), urine analysis for protein with urine dipstick or ratio of protein to creatinine, and blood tests to assess renal and liver function, platelets and haemoglobin depending on the severity of the condition. For pre-eclampsia bloods are taken at least twice weekly if the maternal condition is stable or more frequently if there is any suspicion of clinical deterioration. For chronic hypertension and gestational hypertension, bloods are not routinely taken. Fetal monitoring is done by assessing fetal movements felt by the mother, fetal heart rate monitoring and fetal ultrasound (amniotic fluid measurement, fetal growth, and Doppler velocimetry in the umbilical artery, middle cerebral artery and ductus venosus) (Norwitz 2013).
Indications for delivery of women being managed expectantly would include deterioration of blood pressure control despite antihypertensive treatment, new onset maternal symptoms which include severe headache, blurred vision, epigastric or abdominal pain, vaginal bleeding and a decrease in fetal movements, deterioration in blood tests and a change in fetal condition.
Bed rest (Meher 2005), dietary salt restriction (Meher 2005), vitamin D supplementation (De Regil 2011), vitamin C and E supplementation, and thiazide diuretics are not recommended for prevention of pre-eclampsia (WHO 2011). Calcium supplementation is recommended in areas with low dietary calcium intake (Hofmeyr 2014). Low-dose aspirin, started before 16 weeks, is recommended for the prevention of pre-eclampsia in women who have risk factors for pre-eclampsia (Bujold 2014). Based on expert opinion, severe hypertension during pregnancy should be treated with antihypertensive drugs and the choice of the drug is left to the clinician managing the woman (WHO 2011).
The timing of delivery is based on the severity of the maternal condition, gestational age and fetal condition. The indications for planned early delivery (or contraindications for expectant management) include: instability of maternal condition; persistent severe hypertension unresponsive to medical therapy; persistent progressive or severe headache; visual disturbances; eclampsia; cerebrovascular events; posterior reversible encephalopathy syndrome (PRES); epigastric or abdominal pain; left ventricular failure; pulmonary oedema; severe renal impairment with a creatinine level greater than or equal to 125 μmol/l; the need for dialysis or renal failure; abruptio placenta; non-reassuring fetal testing (non-reassuring fetal heart rate tracing, estimated fetal weight less than fifth centile, oligohydramnios, persistent absent or reversed end-diastolic flow in umbilical artery Doppler); fetal demise; laboratory abnormalities (liver transaminases greater than or equal to 500 IU/L, progressive decrease in platelet count to less than 100 $\times$ 10^9/L, coagulopathy with an INR greater than 2 in the absence of an alternative cause); preterm labour; preterm premature rupture of membranes; HELLP syndrome (Norwitz 2013).
The potential implications for the mother and fetus of expectant management are weighed against the possible complications of an earlier delivery.
Traditionally, the management of hypertensive disorders in pregnancy at or near term (from 34 weeks onwards) has been a planned

early delivery by induction of labour or caesarean section. Currently, there is a tendency in high-income countries to continue with expectant management in the absence of severe pre-eclampsia past 34 0/7 gestational weeks. Canadian guidelines recommend planned early delivery after 37 0/7 weeks in case of pre-eclampsia and expectant management before 34 0/7 weeks. In case of non-severe pre-eclampsia there is insufficient evidence to recommend planned early delivery between 34 0/7 to 36 6/7 weeks (Magee 2008).

Based on a recent literature review by Spong 2011, planned early delivery is recommended:

- at 38 to 39 weeks for women with chronic hypertension on no medications;
- at 37 to 39 weeks for women with chronic hypertension controlled on medications;
- at 36 to 37 weeks for women with chronic hypertension difficult to control;
- at 37 to 38 weeks for women with gestational hypertension;
- at diagnosis for women with severe pre-eclampsia (at or after 34 weeks);
- at 37 weeks for women with mild pre-eclampsia.

How the intervention might work

Planned early delivery by induction of labour or indicated caesarean section is thought to have the following benefits:

- prevention of severe maternal complications in women with hypertensive disorders in pregnancy;
- prevention of poor fetal outcomes and stillbirth.

Potential risks of planned early delivery by induction of labour are:

- increased risk of complications associated with induction of labour such as uterine hyperstimulation and fetal distress;

Potential risks of planned early delivery by induction of labour or caesarean section are:

- concerns related to prematurity. Although the adverse outcomes due to prematurity are uncommon after 34 0/7 weeks of gestation, several recent reports have highlighted increased rates of neonatal morbidity related to respiratory distress syndrome, need for ventilation and neonatal intensive care admission when elective caesarean sections were performed before 39 0/7 weeks of gestation (Maslow 2000; Tita 2009; Wilmink 2010). Infants born between 37 0/7 and 38 6/7 weeks have greater neonatal morbidity during the first year of life in comparison with infants born between 39 0/7 and 41 0/7 weeks (Dietz 2012). Near-term infants have significantly more health problems and increased healthcare costs compared with full-term infants in the first year of life and later on (Boyle 2012; Wang 2004).

The intervention being investigated is timing of delivery. Prolonging gestation may be better for the fetus but it may increase the risks of complications for the mother.

Why it is important to do this review

There are benefits and risks associated with both policies (planned early delivery and expectant management) in women with hypertensive disorders of pregnancy. It is therefore important to establish the safest option associated with more favourable maternal and neonatal outcomes in such cases.

Management of severe pre-eclampsia before term is dealt with in another Cochrane Review comparing interventionist and expectant care (Churchill 2013).

OBJECTIVES

To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with hypertensive disorders, at or near term (from 34 weeks onwards).

METHODS

Criteria for considering studies for this review

Types of studies

We included adequately randomised controlled trials comparing planned early delivery (induction of labour or caesarean section) with expectant management of women with hypertensive disorders from 34 weeks' gestation to term. We would have included cluster-randomised trials but we found none. Studies using a quasi-randomised design are not eligible for inclusion in this review. Similarly, studies using a cross-over design are not eligible for inclusion, because they are not a suitable study design for investigating hypertensive disorders in pregnancy.

Types of participants

Women with hypertensive disorders at 34 weeks 0 days of gestation or longer.

Types of interventions

Comparison of a policy of planned early delivery (by induction of labour or by caesarean section) with a policy of delayed delivery (expectant management).

Types of outcome measures

Primary outcomes

1. Composite maternal outcome, including maternal mortality (death during pregnancy or up to 42 days after delivery) and severe morbidity (eclampsia; cerebral vascular event; pulmonary oedema as defined by trial authors; severe renal impairment, defined as a creatinine level greater than 125 μmol/l or a need for dialysis or urine output less than 0.5 mL/kg/hour for four hours unresponsive to hydration with two intravenous boluses, or as defined by trial authors; liver haematoma or rupture; liver failure, defined as the rapid impairment of synthetic function and development of encephalopathy or as defined by trial authors; haemolysis elevated liver enzymes and low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); thromboembolic disease; and abruptio placentae, defined as a retroplacental clot of more than 15% of the maternal surface or as defined by trial authors).
2. Composite perinatal outcome, including fetal or neonatal death (within six weeks after the expected due date or as defined by trial authors); grade III or IV intraventricular or intracerebral haemorrhage; necrotising enterocolitis (NEC); acute respiratory distress syndrome (ARDS) or grade III/IV hyaline membrane disease; small-for-gestational age (growth below the 10th centile or as defined by trial authors); and neonatal seizures.

Secondary outcomes

Maternal

1. Maternal mortality as described above
2. Eclampsia
3. Cerebrovascular event
4. Pulmonary oedema as defined above
5. Severe renal impairment as defined above
6. Liver haematoma or rupture*
7. Liver failure as defined above
8. HELLP syndrome
9. DIC
10. Thromboembolic disease
11. Abruptio placentae
12. Antepartum haemorrhage
13. Postpartum haemorrhage (blood loss of more than 500 mL or more within 24 hours of delivery)
14. Severe hypertension (systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than 110 mmHg)
15. Caesarean section
16. Assisted delivery (ventouse/forceps)
17. Maternal morbidity of caesarean section (wound infection, wound dehiscence, endometritis, postpartum haemorrhage (blood loss greater than 500 mL), urinary or bowel problems, venous thrombosis)
18. Maternal morbidity related to induction of labour (uterine hyperstimulation, uterine rupture, hyponatraemia, hypotension, chorioamnionitis, cord prolapse, failed induction)
19. Admission to a high care or intensive care unit*
20. Women's experiences and views on the interventions: pregnancy and childbirth experience, physical and psychological trauma, mother-infant interaction and attachment

Fetal and neonatal

1. Fetal death
2. Neonatal death as defined above
3. Grade III or IV intraventricular or intracerebral haemorrhage
4. NEC
5. ARDS or grade III/IV hyaline membrane disease
6. Small-for-gestational age as defined by trial authors
7. Neonatal seizures
8. Apgar score less than seven at five minutes
9. Cord blood pH less than 7.1 or as defined by trial authors
10. Surfactant use*
11. Neonatal intensive care unit or high care unit admission*
12. Intubation and mechanical ventilation or continuous positive airway pressure support
13. Early neonatal sepsis*

Use of health-service resources

1. Duration of hospital stay after delivery for mother
2. Duration of hospital stay after delivery for baby

Economic outcomes

1. Costs to health service resources: short-term and long-term for both mother and baby
2. Costs to the woman, her family, and society

* denotes that outcome was not specified in this review's protocol and was added at the review stage.

Search methods for identification of studies

The following Methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (1 January 2016). The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals

and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies).

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following Methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and did not need to consult a third person.

We included one study published in abstract only, as it was assessed as eligible (Majeed 2014).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion and did not need to consult a third person. We entered data into Review Manager 5 software (RevMan 2014) and checked them for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion and did not need to involve a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and are unlikely to influence the outcome; missing data have been imputed using appropriate methods);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

We assessed the quality of the evidence using the GRADE approach, as outlined in the GRADE Handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison (Planned early delivery versus expectant management (all women)):

1. Composite maternal outcome including maternal mortality (death during pregnancy or up to 42 days after delivery) and severe morbidity (eclampsia; cerebral vascular event; pulmonary oedema, as defined by trial authors; severe renal impairment, defined as a creatinine level greater than 125 μmol/l or a need for dialysis or urine output less than 0.5 mL/kg/hour for four hours unresponsive to hydration with two intravenous boluses, or as defined by trial authors; liver haematoma or rupture; liver failure, defined as the rapid impairment of synthetic function and development of encephalopathy or as defined by trial authors; haemolysis elevated liver enzymes and low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); thromboembolic disease; and abruptio placentae, defined as a retroplacental clot of more than 15% of the maternal surface or as defined by trial authors).
2. Composite perinatal outcome including fetal or neonatal death (within six weeks after the expected due date or as defined by trial authors); grade III or IV intraventricular or intracerebral haemorrhage; necrotizing enterocolitis (NEC); acute respiratory distress syndrome (ARDS) or grade III/IV hyaline membrane disease; small-for-gestational age (growth below the 10th centile or as defined by trial authors); and neonatal seizures.
3. Caesarean section.
4. Duration of hospital stay for mother after delivery.
5. Duration of hospital stay for fetus after delivery.

GRADEpro Guideline Development Tool was used to import data from Review Manager 5 (RevMan 2014) in order to create

'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes, using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as a summary risk ratio (RR) with a 95% confidence interval (CI).

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but using different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials in the analyses. If we had, we would have followed Chapter 16.3 of *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to perform analysis of cluster-randomised trials. We would have calculated the intra-cluster correlation coefficient (ICC) and design effect. We would have multiplied the standard error of the effect estimate (from analysis ignoring clustering) by the square root of the design effect. We would have performed meta-analysis using the inflate variances and the generic inverse-variance method (Chapter 16.3.6 Higgins 2011).

Cross-over trials

Cross-over trials are inappropriate for this intervention.

Multi-armed trials

We did not identify any multi-armed trials. If we had, we would have combined all relevant experimental intervention groups of the study into a single group and all relevant control intervention groups into a single control group when we analysed the data. If we had considered one of the arms irrelevant, we would have excluded it from analysis.

Dealing with missing data

For included studies, we noted levels of attrition. We did not need to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

There were fewer than 10 studies in the meta-analysis. In future updates of this review, if there are 10 or more studies in a meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager 5 software (RevMan 2014). We used a fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detected substantial statistical heterogeneity, we would have used a random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. We would have treated the random-effects summary as the average range of possible treatment effects and we would have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not combine trials.

Where we use random-effects analyses, we present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we had identified substantial heterogeneity, we would have investigated it using subgroup analyses and sensitivity analyses. We would have considered whether an overall summary is meaningful, and if it was, we would have used random-effects analysis to produce it.

We carried out the following subgroup analyses:

1. Women at 34 weeks 0 days to 36 weeks 6 days of gestation versus 37 weeks 0 days to 38 weeks 6 days versus more then 39 weeks of gestation.
2. Each gestational week.
3. Women with pre-eclampsia only versus women with gestational hypertension (mild, not severe) only or pre-existing hypertension only.

We used the following primary outcomes in subgroup analysis.

1. composite maternal
2. composite perinatal outcome

Broekhuijsen 2015 has not yet published the composite outcomes by gestational age, so we also carried out subgroup analysis using the outcome respiratory distress syndrome.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We did not need to perform sensitivity analysis for primary outcomes, as we did not identify substantial heterogeneity in the included studies.

It was not indicated to perform sensitivity analyses for aspects of the review that might affect the results; for example, where there is a risk of bias associated with the quality of some of the included trials; or to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity; and to explore the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

We would have used the following outcomes in sensitivity analyses.

1. Composite maternal outcome.
2. Composite perinatal outcome.

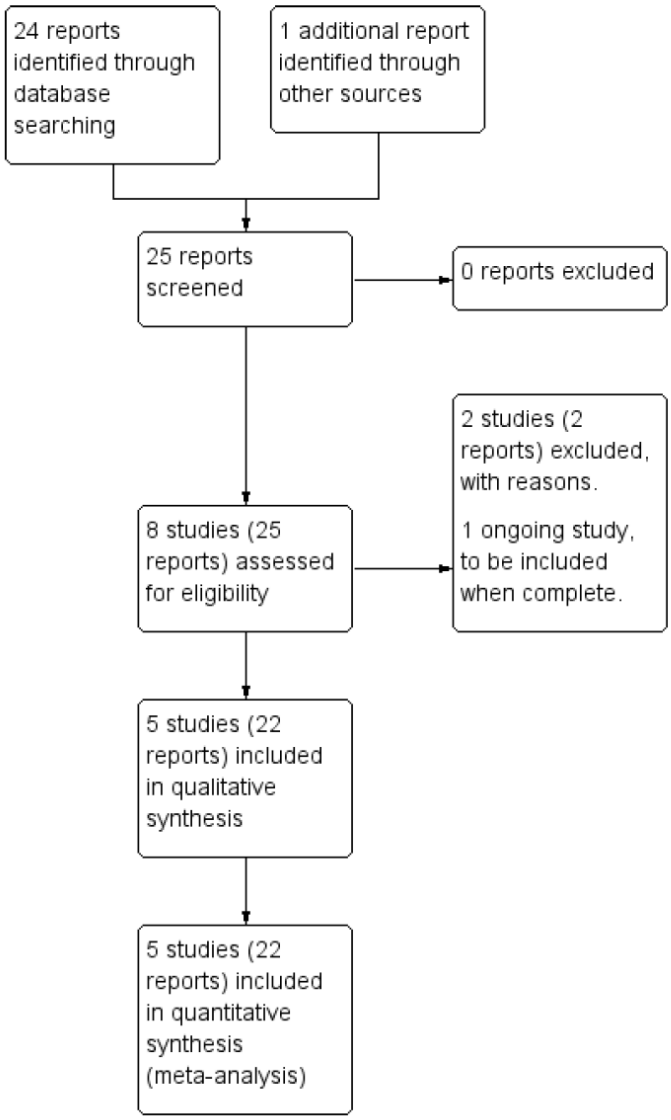
RESULTS

Description of studies

Results of the search

The search of Cochrane Pregnancy and Childbirth's Register retrieved 24 trial reports, and we found one additional report through other sources. These reports corresponded to eight studies. Five of these studies (22 reports) fulfilled the eligibility criteria for the review (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Majeed 2014; Owens 2014). Two studies (two reports) were excluded (Ramrakhyani 2001; Tukur 2007), and one study (Shennan 2013) is ongoing and will be eligible for inclusion when it is complete (*See:* Figure 1).

Figure 1. Study flow diagram.



Included studies

We included five studies (involving 1819 women) in this review (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Majeed 2014; Owens 2014). *See* Characteristics of included studies.

Design

All five of the included studies were two-arm randomised controlled trials, comparing planned early delivery with expectant management for hypertensive disorders from 34 weeks to term.

Sample sizes

Two of the studies were large multicentre trials (Broekhuijsen 2015; Koopmans 2009), which recruited 704 and 756 women respectively. Hamed 2014 recruited 76 women at two hospitals. Two studies took place in a single centre, recruiting 100 women (Majeed 2014), and 183 women (Owens 2014).

Setting

The two large multicentre trials were conducted in the Netherlands (Broekhuijsen 2015; Koopmans 2009). Three smaller studies were carried out in India (Majeed 2014), USA (Owens 2014), and Saudi Arabia and Egypt (Hamed 2014).

Participants

The gestational age ranges of women eligible for the studies were 36 to 41 weeks (Koopmans 2009), 36 to 40 weeks (Majeed 2014), 34 to 37 weeks (Broekhuijsen 2015; Owens 2014), and 24 to 36 weeks (Hamed 2014).

The type of hypertensive disorder included varied between studies: Koopmans 2009 and Majeed 2014 included pregnant women with gestational hypertension or mild pre-eclampsia, Owens 2014 included women with mild pre-eclampsia only, Broekhuijsen 2015 recruited women with gestational hypertension, mild pre-eclampsia or deteriorating chronic hypertension. Hamed 2014 was the only trial to concentrate on women with chronic hypertension (mild to moderate, without proteinuria, diagnosed before 20 weeks' gestation or if the woman was known to be hypertensive before pregnancy). Women were not eligible to participate in this study if they had gestational hypertension or new onset of pre-eclampsia where previously normotensive, in contrast to Owens 2014 and Koopmans 2009 where only women who had newly identified hypertension could participate.

Of the studies that included women with pre-eclampsia, they all excluded women with severe pre-eclampsia. Broekhuijsen 2015 and Koopmans 2009 excluded women who had a diastolic blood pressure $\geq$ 110 mmHg despite medication, a systolic blood pressure $\geq$ 170 mmHg despite medication, proteinuria $\geq$ 5 g per 24 hours, eclampsia, HELLP syndrome, pulmonary oedema or cyanosis, oliguria less than 500 mL in 24 hours, renal disease, heart disease, and severe pre-eclamptic complaints such as frontal headache or ruptured membranes. Majeed 2014 excluded women if the systolic blood pressure was above 160 mmHg, if the diastolic blood pressure was above 110 mmHg or if there was more than 5 g proteinuria per 24-hour collection. Owens 2014 excluded all that did not have mild pre-eclampsia.

Studies had different inclusion and exclusion criteria for participants, some concerning factors that may be related to, or result from, hypertensive disorders. For example, multiple pregnancies, pre-existing diabetes, and suspected intrauterine growth restriction. Broekhuijsen 2015 had the most inclusive eligibility criteria, potentially meaning that the population of women recruited to this study were more representative of women with hypertensive disorders. Multiple pregnancies were excluded from Hamed 2014, Koopmans 2009 and Owens 2014, but not excluded in Broekhuijsen 2015. In this study, 44 participants out of 703 had multifetal gestations (18 out of 352 randomised to planned early delivery, 26 out of 351 randomised to expectant monitoring), and the infant outcomes were deemed present if at least one neonate was affected. Women with diabetes mellitus were excluded from Hamed 2014, Koopmans 2009 and Owens 2014, but not excluded from Broekhuijsen 2015. Women who had a previous caesarean section were excluded from Hamed 2014 and Koopmans 2009, but not excluded from Broekhuijsen 2015. Babies with suspected intrauterine growth restriction or small-for-gestational age were excluded from Koopmans 2009 and Owens 2014, but were not excluded from Broekhuijsen 2015. Women taking antihypertensive medication were excluded from Owens 2014, excluded if the medication was intravenous in Koopmans 2009, and eligible to participate in Broekhuijsen 2015. Majeed 2014 did not describe the exclusion criteria or detailed inclusion criteria.

Interventions

Two studies compared an intervention group who had labour induced before term: at 34 to 36 weeks' gestation (Broekhuijsen 2015) and at 34 to 37 weeks (Owens 2014), with a comparison group who were monitored until 37 weeks' gestation when induction began, if labour had not started spontaneously. Three studies compared induction of labour at term or closer to term: at 37 completed weeks (Hamed 2014) and at 36 to 41 weeks (Koopmans 2009; Majeed 2014) in the intervention group, with a comparison group who were monitored until 41 weeks when induction began, if labour had not started spontaneously.

In the intervention groups, infants were delivered by induction of

labour, or by caesarean section if necessary. Three studies placed a time limit on this intervention, within 12 hours (Owens 2014) or 24 hours (Broekhuijsen 2015; Koopmans 2009) of randomisation. Labour was induced and augmented with amniotomy and oxytocin (Broekhuijsen 2015; Hamed 2014; Koopmans 2009). If necessary cervical ripening was stimulated with intracervical or intravaginal prostaglandins or a balloon catheter (Broekhuijsen 2015; Koopmans 2009) or with vaginal misoprostol (Hamed 2014).

Women in the expectant management group were monitored as outpatients (Hamed 2014), inpatients (Owens 2014), or in an inpatient or outpatient setting depending on their condition (Broekhuijsen 2015; Koopmans 2009). Monitoring consisted of measuring maternal blood pressure and screening of urine for protein (Broekhuijsen 2015; Hamed 2014; Koopmans 2009), looking for signs of disease progression with severe features of pre-eclampsia (Owens 2014), mother's assessment of fetal movements and electronic fetal heart rate monitoring (Broekhuijsen 2015; Koopmans 2009), non-stress testing (Owens 2014), and ultrasound examination (Koopmans 2009). Majeed 2014 did not provide information on the nature of the monitoring.

Outcomes

The two largest trials (Broekhuijsen 2015; Koopmans 2009) reported the composite outcome for maternal mortality and morbidity, and a composite outcome for perinatal mortality and morbidity, defined as the primary outcomes in this review. In addition, these trials reported maternal and infant mortality and morbidity outcomes individually. Maternal mortality was not reported by the other three trials (Hamed 2014; Majeed 2014; Owens 2014), and two trials did not report perinatal mortality (Majeed 2014; Owens 2014).

All studies reported on disease progression, for example, the development of severe hypertension, defined in a variety of ways (Hamed 2014; Koopmans 2009; Owens 2014), eclampsia (Broekhuijsen 2015; Koopmans 2009), HELLP syndrome (Broekhuijsen 2015; Koopmans 2009; Owens 2014), and acute renal failure (Majeed 2014). Adverse infant outcomes were reported for all trials except Majeed 2014. These include possible consequences of early delivery for the infants, such as respiratory distress syndrome (Broekhuijsen 2015; Koopmans 2009; Owens 2014), and neonatal intensive care unit admission (Broekhuijsen 2015; Hamed 2014; Koopmans 2009; Owens 2014).

Majeed 2014 was presented as a poster abstract, and the data were therefore limited. We contacted the authors for additional information, but have not received a reply. The most comprehensive reporting of outcomes was by Broekhuijsen 2015 and Koopmans 2009, with both trials presented across multiple published reports.

Funding sources

Two studies (Broekhuijsen 2015; Koopmans 2009) were funded by ZonMw, the Netherlands Organisation for Health Research and Development. Hamed 2014 and Owens 2014 were both funded through their affiliated universities: Qassim University and the University of Mississippi Medical Centre, respectively. As Majeed 2014 was presented as a poster abstract, with limited information given, it is not clear who provided funding for this study.

Declarations of interest

None of the study authors declared any conflicts of interest. This was not mentioned in Majeed 2014.

Excluded studies

We excluded two studies (two reports); one because it was not a randomised controlled trial, with group allocation based on gestational age at presentation (Ramrakhyani 2001), and the other compared two methods of planned early delivery: caesarean section and induction with vaginal misoprostol (Tukur 2007). See Characteristics of excluded studies.

Ongoing studies

We found one ongoing study (Shennan 2013). This trial compares planned early delivery with monitoring until induction at 37 weeks' gestation, for pregnant women with pre-eclampsia between 34 and 37 weeks of gestation. According to the protocol, recruitment started in April 2014, and it was anticipated that it will take approximately three years to recruit 900 women. See Characteristics of ongoing studies.

Risk of bias in included studies

Assessment of the methodological quality of the included studies was based on risk of bias in relation to selection bias (method of randomisation and allocation concealment), performance bias, detection bias, attrition bias (loss of participants from the analyses) and reporting bias. A summary of 'Risk of bias' assessments for each study, and for included trials overall, are set out in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

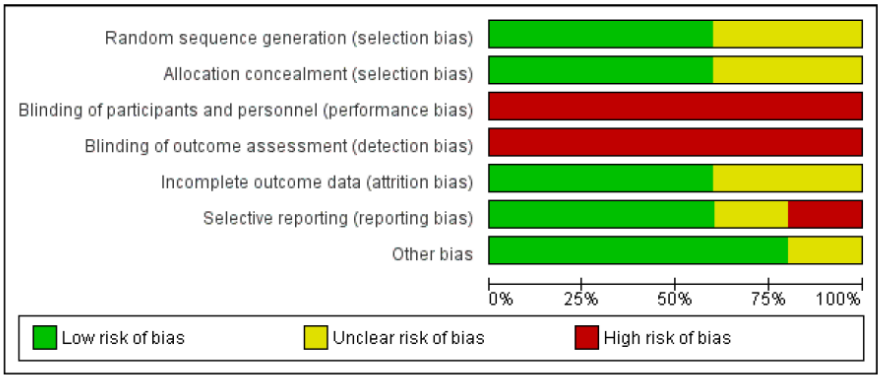
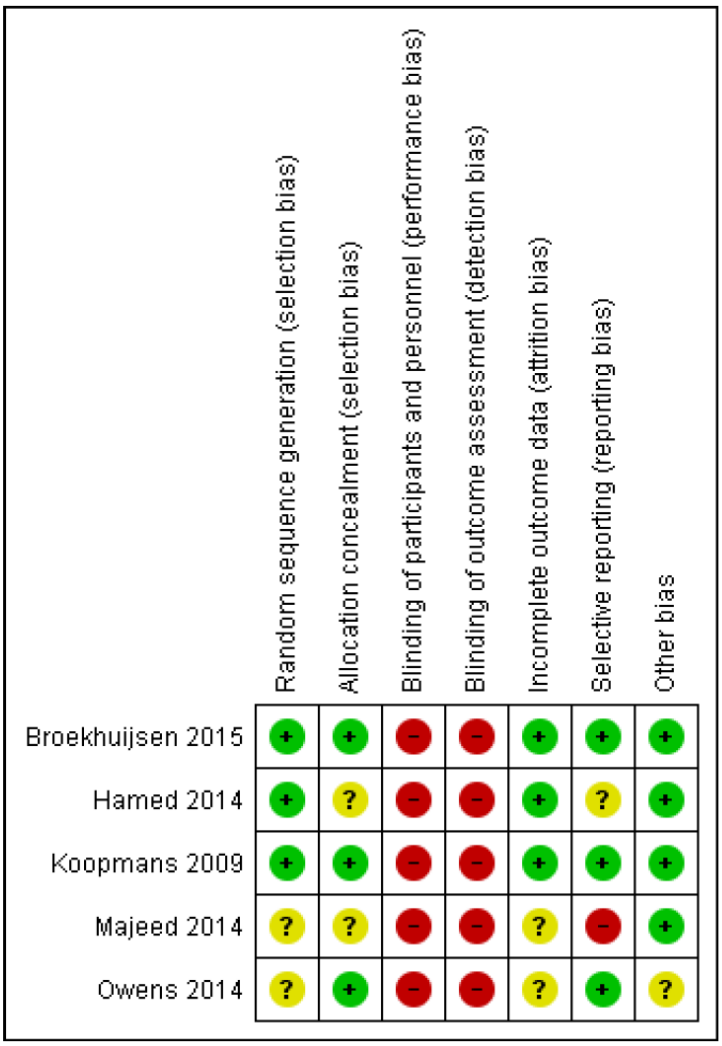


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of the randomisation sequence

Three studies reported using a computerised or web-based random-number generator to generate the randomisation sequence, which we judged were at low risk of bias (Broekhuijsen 2015; Hamed 2014; Koopmans 2009). We judged the remaining two studies to be at unclear risk of bias: Owens 2014 described using stratified and random permuted blocks of two but did not describe how the randomisation sequence was generated, and Majeed 2014 did not mention the method for determining the randomisation sequence.

Allocation concealment

In two of the studies, the method for concealing group allocation at the point of randomisation was not clear (Hamed 2014; Majeed 2014). Three studies were at low risk of bias: Owens 2014 concealed allocation in sealed envelopes, and the web-based central allocation of Broekhuijsen 2015 and Koopmans 2009 concealed their allocation.

Blinding

The blinding of women and health professionals was not possible for this intervention. This may have had an effect on other treatment decisions. All included studies have consequently been assessed as high risk of bias due to lack of blinding.

Incomplete outcome data

We considered the risk of bias to be low in Broekhuijsen 2015, Hamed 2014 and Koopmans 2009, as all women were accounted for and there was little or no attrition. The number of women allocated to each group was not reported by Majeed 2014, so we judged the risk of bias to be unclear as we cannot assess whether data for all women are reported. There was some attrition from Owens 2014, and the data were not presented as intention-to-treat, so we considered that the risk of bias is also unclear for this trial.

Selective reporting

Protocols were available for Broekhuijsen 2015, Koopmans 2009 and Owens 2014. All prespecified outcomes were reported for these trials, so we judged these to be at a low risk of reporting bias. Reporting appeared to be good in Hamed 2014, however no protocol was available to assess whether all prespecified outcomes were reported, so risk of bias was unclear. Majeed 2014 was assessed from a poster-presentation abstract, which only reported significant findings, and was therefore at high risk of bias.

Other potential sources of bias

Owens 2014 was stopped early due to a change in hospital policy, at 74% of the enrolment target, leaving the study underpowered to demonstrate statistically significant differences, with unclear implications for the risk of other bias. The baseline characteristics of women assigned to the planned delivery and expectant monitoring groups appear to be similar in all studies, so there is low risk of other potential sources of bias for Broekhuijsen 2015, Hamed 2014, Koopmans 2009, and Majeed 2014.

Effects of interventions

See: **Summary of findings for the main comparison** Planned early delivery versus expectant management for hypertensive disorders from 34 weeks' gestation to term

Planned early delivery versus expectant management

See Summary of findings for the main comparison. We included five studies, involving 1819 women.

Primary outcomes

Two studies reported the**composite maternal outcome, including maternal mortality and severe morbidity** (Broekhuijsen 2015; Koopmans 2009). There was a lower risk of these severe adverse outcomes for women randomised to planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women, *evidence graded high*, Analysis 1.1). There were no clear differences between groups based on our subgroup analysis by gestational age, gestational week or condition (see Analysis 2.1; Analysis 3.1; Analysis 4.1).

The same two studies also reported the **composite perinatal outcome (including fetal or neonatal death and serious morbidity)**. There was not enough information to draw any conclusions about the effects on neonatal mortality and serious morbidity. Meta-analysis was not possible, due to substantial heterogeneity (I^2 = 87%, Tau^2 = 0.98) for this outcome between these two studies (1459 infants, Analysis 1.2). It is worth noting that Broekhuijsen 2015 found that infants in the planned early delivery group had a higher risk of respiratory distress syndrome than those in the expectant management group (RR 3.32, 95% CI 1.35 to 8.18, 703 infants, Analysis 2.2) with planned early delivery taking place at 34 to 37 weeks' gestation. However Koopmans 2009 showed

no evidence of differences in composite infant mortality and morbidity (RR 0.77, 95% CI 0.46 to 1.28, 756 infants, Analysis 2.3) with planned early delivery taking place later, at 36 to 41 weeks' gestation. There were no clear differences between groups based on our subgroup analysis by gestational age or gestational week (see Analysis 2.3; Analysis 3.2; Analysis 3.3). However Broekhuijsen 2015 have not yet published the composite outcomes by gestational age, so any possible adverse effects on infants born at the earliest gestations have not yet been explored.

Secondary outcomes

Maternal

There were no incidences of **maternal mortality** in the two studies that reported it (1457 women, Analysis 1.3). We found no clear differences between delivery and expectant management for the number of women experiencing **eclampsia** (RR 0.20, 95% CI 0.01 to 4.14, 1459 women, two studies, Analysis 1.4). There were no events reported for **pulmonary oedema** (703 women, one study, Analysis 1.5). Women who were assigned planned early delivery had a lower risk of **severe renal impairment** (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study, Analysis 1.6), and **HELLP syndrome** (RR 0.40, 95% CI 0.17 to 0.93, 1628 women, three studies, Analysis 1.7) than women assigned to expectant management. We found no clear differences between planned early delivery and expectant management for the number of women experiencing **thromboembolic disease** (RR 1.67, 95% CI 0.22 to 12.58, 1459 women, two studies, Analysis 1.8), **abruptio placentae** (RR 0.64, 95% CI 0.17 to 2.34, 1535 women, three studies, Analysis 1.9), or **postpartum haemorrhage** (RR 0.88, 95% CI 0.57 to 1.35, 741 women, one study, Analysis 1.10).

There was high heterogeneity between studies for women developing **severe hypertension** (I^2 = 79%, Tau^2 = 0.83). There was not enough information to draw any conclusions about the effects on severe hypertension (995 women, three studies, Analysis 1.11). Two studies (919 women) reporting this outcome found that planned early delivery was less likely to result in the progression to severe hypertension, while one study (74 women) found no difference. The study that found no difference had recruited pregnant women with chronic hypertension (Hamed 2014), while the women in the other two studies had mild pre-eclampsia (Owens 2014), gestational hypertension or mild pre-eclampsia (Koopmans 2009).

We found no clear differences between planned early delivery and expectant management for **caesarean section** (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, *evidence graded moderate,* Analysis 1.12), **assisted delivery (ventouse/forceps)** (RR 0.93, 95% CI 0.70 to 1.24, 1459 women, two studies, Analysis 1.13), or **endometritis (maternal morbidity of caesarean section)** (RR 0.75, 95% CI 0.17 to 3.35, 756 women, one study, Analysis 1.14). There were no events reported for **uterine rupture (maternal morbidity related to induction of labour)** (756 women, one study, Analysis 1.15). We found no clear differences between planned early delivery and expectant management for maternal **admission to a high care or intensive care unit** (RR 0.41, 95% CI 0.16 to 1.07, 708 women, one study, Analysis 1.16).

Women's experiences and views on the interventions were not reported in any of the included studies. However, Koopmans 2009 assessed women's health-related quality of life after planned early delivery or expectant management. They administered the Short-Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression Scale (HADS), and Symptom Checklist (SCL-90). Measurements were at baseline, six weeks postpartum and six months postpartum. They found no clear difference in these measures of health-related quality of life. (The numeric results are not presented in this review, because the outcomes do not correspond to those prespecified in the protocol. However, as these are important issues we have included this narrative summary of the results).

Several of the outcomes for this review were not reported by trial authors: **cerebrovascular event, liver haematoma or rupture, liver failure as defined above, dissemination intravascular coagulation,** and **antepartum haemorrhage.**

Fetal and neonatal

One study reported**fetal death**, with no events (756 infants, Analysis 1.17). There were very few events, and therefore not enough information to see if there was a difference in **neonatal death** (RR 2.00, 95% CI 0.19 to 21.14, 1535 infants, three studies, Analysis 1.18) and **grade III or IV intraventricular or intracerebral haemorrhage** (RR 6.92, 95% CI 0.36 to 133.41, 674 infants, one study, Analysis 1.19). We found no clear difference in the numbers of infants with **nectrotising enterocolitis** (RR 0.98, 95% CI 0.14 to 6.89, 1338 infants, two studies, Analysis 1.20). Babies allocated to planned early delivery had a higher risk of **acute respiratory distress syndrome or grade III/IV hyaline membrane disease** (RR 2.24, 95% CI 1.20 to 4.18, 1511 infants, three studies, Analysis 1.21). There was no clear difference between groups assigned to planned early delivery or expectant monitoring for **small-for-gestational age** as defined by trial authors (RR 1.58, 95% CI 0.89 to 2.79, 1001 infants, three studies, Analysis 1.22), **neonatal seizures** (RR 3.97, 95% CI 0.45 to 35.30, 699 infants, one study, Analysis 1.23), **Apgar score less than seven at five minutes** (RR 1.11, 95% CI 0.60 to 2.05, 1454 infants, two studies, Analysis 1.24), and **cord blood pH less than 7.1** or as defined by trial authors (RR 0.58, 95% CI 0.31 to 1.09, 1145 infants, two studies, Analysis 1.25). In the one study that reported **surfactant use**, no infants required it (639 infants, Analysis 1.26). Babies in the group allocated to planned early delivery were more likely to be **admitted to neonatal intensive care unit or high care unit** than those allocated to expectant management (RR 1.65,

95% CI 1.13 to 2.40, 1585 infants, four studies, Analysis 1.27). **Intubation and mechanical ventilation or continuous positive airway pressure support** was not reported in any of the included studies. There was a substantial difference in the incidence of **early neonatal sepsis** between the two studies that reported it, so results have not been pooled (1455 infants, two studies, Analysis 1.28).

Use of health-service resources

There was no clear difference in the **duration of hospital stay after delivery for mother** (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15; 925 women, two studies, *evidence graded moderate,* Analysis 1.29), and no clear difference in the **duration of hospital stay after delivery for baby** (MD -0.20 days, 95% CI -0.57 to 0.17, 756 infants, one study, *evidence graded moderate,* Analysis 1.30).

Economic outcomes

The **costs to health service resources: short-term and long-term for both mother and baby** and **costs to the woman, her family, and society** were not reported in the included studies.

DISCUSSION

Summary of main results

We included five studies involving 1819 women, comparing planned early delivery versus expectant management for hypertensive disorders from 34 weeks to term.

Fewer women who had hypertensive disorders of pregnancy experienced severe adverse outcomes (composite maternal mortality and severe morbidity) when they were allocated to planned early delivery. Planned early delivery was also associated with lower levels of HELLP syndrome and severe renal impairment. There was no clear difference in any of the other maternal outcomes reported by the included studies.

There was not enough information to draw any conclusions about the effects on neonatal mortality and severe morbidity, as there were limited data assessing all hypertensive disorders as one group. Planned early delivery was associated with higher levels of respiratory distress syndrome, and NICU admission. There was no clear difference for other infant outcomes reported by the included studies.

No difference was shown between planned early delivery and expectant management in the proportion of women needing a caesarean section, and in the duration of hospital stay after delivery for mother or baby.

(See Summary of findings for the main comparison.)

Overall completeness and applicability of evidence

The studies included in this review addressed the objective, which was to determine the risks and benefits of expectant management versus planned early delivery for the hypertensive disorders of pregnancy after 34 weeks gestation. The management of pre-eclampsia diagnosed before 34 weeks is described in another Cochrane Review (Churchill 2013). The majority of women included in this review had mild pre-eclampsia and gestational hypertension, with fewer women having chronic hypertension. Most of the women included came from the Netherlands, with smaller numbers from India, USA and Saudi Arabia, making the review globally applicable. The results are applicable to general obstetric practice when the hypertensive disorders of pregnancy are considered together, but an individual patient meta-analysis may provide more answers as it would allow for more statistical power when reviewing the different types of hypertensive disorders in pregnancy.

Quality of the evidence

Two fairly large, well-designed trials contributed the majority of the evidence to this review (Broekhuijsen 2015; Koopmans 2009). Due to the nature of the intervention, no studies attempted to blind participants or clinicians to group allocation. We did not downgrade studies for this; however, women and staff would have been aware of the intervention and this may have affected aspects of care and decision-making, for example, whether to carry out a caesarean section.

We graded the level of evidence as high (composite maternal mortality and morbidity), moderate (caesarean section, duration of hospital stay after delivery for mother, and duration of hospital stay after delivery for baby), or low (composite infant mortality and morbidity) (see Summary of findings for the main comparison). Where the evidence was downgraded, it was mostly because the CIs were wide, crossing both the line of no effect and appreciable benefit or harm.

Potential biases in the review process

The assessment of risk of bias involves subjective judgements. This potential limitation is minimised by following the procedures in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with review authors independently assessing studies and resolving any disagreement through discussion, and if required involving a third assessor in the decision.

Agreements and disagreements with other studies or reviews

The findings of this review show that planned early delivery for hypertensive disorders of pregnancy are associated with less severe maternal adverse outcomes. This analysis looks at all the hypertensive diseases, namely chronic hypertension, gestational hypertension and mild pre-eclampsia as one group. The National Institute for Health and Clinical Excellence guidelines on hypertension in pregnancy: diagnosis and management (NICE 2010), the American College of Obstetricians and the Society for Maternal-Fetal Medicine and Gynecologists Committee opinion number 560 on medically indicated late-preterm and early term deliveries (ACOG No. 560 2013) and the Society of Obstetric Medicine of Australia and New Zealand guideline for the management of hypertensive disorders of pregnancy (Lowe 2014) set different gestational ages for delivery based on the hypertensive condition.

AUTHORS' CONCLUSIONS

Implications for practice

For hypertensive disorders as a group, based on the limited data available for this review, planned early delivery appears to be better for the mother after 34 weeks' gestation. However, it is unclear whether planned early delivery increases risks for the baby, especially at earlier gestations, and more data are needed to guide practice. It is also unclear whether planned early delivery is advisable for different hypertensive conditions. Further studies are needed to look at the individual conditions before this is implemented into clinical practice.

Implications for research

Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions. These studies should include the maternal outcomes of mortality and severe morbidity like eclampsia, a cerebral vascular event, pulmonary oedema, severe renal impairment, a liver haematoma or rupture, liver failure, HELLP syndrome, DIC, thromboembolic disease and abruptio placentae. Perinatal outcomes that should be included are fetal or neonatal death, grade III or IV intraventricular or intracerebral haemorrhage, NEC, ARDS or grade III/IV hyaline membrane disease, small-for-gestational age and neonatal seizures. The outcomes of the incidence of caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby should also be included.

An individual patient meta-analysis on the data currently available would provide further information on the outcomes of the different types of hypertensive disease encountered in pregnancy.

ACKNOWLEDGEMENTS

Denise Atherton for administrative assistance; Lynn Hampson for the literature search.

CC's contribution to this project was supported by the Discovery Foundation and the South African Medical Association.

HW's contribution to this project was supported by the National Institute for Health Research, via Cochrane Programme Grant funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

The Cochrane generic protocol on Interventions for preventing pre-eclampsia and its consequences (Meher 2005) was used in preparation of the protocol for this review.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

This project was supported by the National Institute for Health research, via Cochrane Infrastructure and Cochrane Programme Grant funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Broekhuijsen 2015 *{published data only}*

Broekhuijsen K, Langenveld J, Van Baaren G, Van Pampus MG, Van Kaam AH, Groen H, et al. Correction: Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial. *BMC Pregnancy and Childbirth* 2013;**13**:232.

* Broekhuijsen K, Van Baaren GJ, Van Pampus M, Ganzevoort W, Sikkema M, Woiski M, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015;**385**:2492–501.

Broekhuijsen K, Van Baaren GJ, Van Pampus M, Sikkema M, Woiski M, Oudijk M, et al. Delivery versus expectant

monitoring for late preterm hypertensive disorders of pregnancy (HYPITAT-II): a multicenter, open label, randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2014;**210**(1 Suppl):S2.

Langenveld J, Broekhuijsen K, Van Baaren GJ, Van Pampus MG, Van Kaam AH, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): A multicentre, open-label randomised controlled trial. *BMC Pregnancy and Childbirth* 2011;**11**: 50.

Hamed 2014 *{published data only}*

Hamed HO, Alsheeha MA, Abu-Elhasan AM, Elmoniem AEA, Kamal MM. Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery. *International Journal of Gynecology and Obstetrics* 2014;**17**: 15–20.

Koopmans 2009 *{published data only}*

Bijlenga D, Birnie E, Mol B, Bekedam D, De Boer K, Drogtop A, et al. Health-related quality of life after induction of labor or expectant management in pregnancy-induced hypertension and pre-eclampsia at term. *Hypertension in Pregnancy* 2008;**27**(4):518.

Bijlenga D, Koopmans CM, Birnie E, Mol BWJ, Van der Post JA, Bloemenkamp KW, et al. Health-related quality of life after induction of labor versus expectant monitoring in gestational hypertension or preeclampsia at term. *Hypertension in Pregnancy* 2011;**30**(3):260–74.

Hermes W, Koopmans CM, Van Pampus MG, Franx A, Bloemenkamp KW, Van der Post J, et al. Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: do women's postpartum cardiovascular risk factors differ between the two strategies?. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2013;**171**(1):30–4.

Koopmans C, Ven den Berg P, Moll BW, Groen H, Willekes, Kwee A, et al. Pregnancy-induced hypertension and preeclampsia after 36 weeks: induction of labour versus expectant monitoring. The HYPITAT trial. *Hypertension in Pregnancy* 2008;**27**(4):421.

Koopmans CM, Bijlenga D, Aarnoudse JG, Van Beek E, Bekedam DJ, Van den Berg PP, et al. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial. *BMC Pregnancy and Childbirth* 2007;**7**:14.

* Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009;**374**(9694):979–88.

Tajik P, Van der Tuuk K, Koopmans C, Groen H, Van Pampus M, Van der Berg P, et al. Should cervical ripeness play a role in the decision for labor induction in women with gestational hypertension or mild preeclampsia at term: an exploratory analysis of the HYPITAT trial. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1): S349.

Tajik P, Van der Tuuk K, Koopmans CM, Groen H, Van Pampus MG, Van der Berg PP, et al. Should cervical favourability play a role in the decision for labour induction in gestational hypertension or mild pre-eclampsia at term? An exploratory analysis of the HYPITAT trial. *BJOG: an international journal of obstetrics and gynaecology* 2012;**119** (9):1123–30.

Van Der Tuuk K, Koopmans C, Aarnoudse J, Rijnders R, Van Beek J, Porath M, et al. Prediction of deterioration of the clinical condition in women with preeclampsia or pregnancy induced hypertension at term. *Hypertension in Pregnancy* 2008;**27**(4):464.

Van Pampus M. Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labour versus expectant monitoring. A comparison of maternal and neonatal outcome, maternal quality of life and costs. Netherlands Trial Register (www.trialregister.nl) (accessed 1 November 2005).

Vijgen S, Koopmans C, Opmeer B, Groen H, Bijlenga D, Aarnoudse J, et al. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). *BJOG: an international journal of obstetrics and gynaecology* 2010;**117**:1577–85.

Vijgen S, Opmeer B, Mol BW, Bijlenga D, Burggraaff J, Van Loon A, et al. An economic analysis of induction of labor and expectant management in women with pregnancy-induced hypertension or preeclampsia at term (HYPITAT Trial). *Hypertension in Pregnancy* 2008;**27**(4):519.

Visser S, Hermes W, Koopmans C, Van Pampus MG, Franx A, Mol BW, et al. Hypertension 6 weeks and 21/2 years after term pregnancies complicated by hypertensive disorders. *Reproductive Sciences* 2011;**18**(3 Suppl 1):354A.

Majeed 2014 *{published data only}*

Majeed A, Kundu S, Singh P. Study on induction of labour versus expectant management in gestational hypertension or mild preeclampsia after 36 weeks of gestation. *BJOG: an International Journal of Obstetrics and Gynaecology* 2014;**121** (Suppl 2):118.

Owens 2014 *{published data only}*

Martin JN, Owens MY, Thigpen B, Parrish MR, Keiser SD, Wallace K. Management of late preterm pregnancy complicated by mild preeclampsia: A prospective randomized trial. *Pregnancy Hypertension* 2012;**2**(3):180.

NCT00789919. Mild preeclampsia near term: deliver or deliberate?. clinicaltrials.gov/ct2/show/NCT00789919 Date first received: 12 November 2008.

* Owens MY, Thigpen B, Parrish MR, Keiser SD, Sawardecker S, Wallace K, et al. Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks?. *Journal of the Mississippi State Medical Association* 2014;**55**(7): 208–11.

References to studies excluded from this review

Ramrakhyani 2001 *{published data only}*
Ramrakhyani N, Sharma SK, Sankhla J, Sharma SK. Role of active management of pregnancy with hypertension in improving maternal and foetal outcome. *Journal of the Association of Physicians of India* 2001;**49**(1):Abstract no: 149.

Tukur 2007 *{published data only}*
Tukur J, Umar NI, Khan N, Musa D. Comparison of emergency caesarean section to misoprostol induction for the delivery of antepartum eclamptic patients: a pilot study. *Nigerian Journal of Medicine* 2007;**16**(4):364–7.

References to ongoing studies

Shennan 2013 *{published data only}*
ISRCTN01879376. PHOENIX - Pre-eclampsia in HOspital: Early iNductIon or eXpectant management. isrctn.com/ISRCTN01879376 Date first received: 20 November 2013.

Additional references

Abalos 2013
Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2013;**170**(1):1–7. [doi: 10.1016/j.ejogrb.2013.05.005]

ACOG Hypertension in Pregnancy 2013
Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstetrics and Gynecology* 2013;**122**(5):1122–31.

ACOG No. 560 2013
Committee Opinion No. 560. American College of Obstetricians and Gynaecologists. Medically indicated late-preterm and early-term deliveries. Obstetrics and Gynecology 2013; Vol. 121, issue 4:908–10.

August 2012
August P, Sibai BM. Preeclampsia: Clinical features and diagnosis. www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis (accessed 10 March 2014).

Barton 2001
Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *American Journal of Obstetrics and Gynecology* 2001;**184**(5):979–83.

Belizan 1980
Belizan JM, Villar J. The relationship between calcium intake and edema, proteinuria, and hypertension-gestosis: an hypothesis. *American Journal of Clinical Nutrition* 1980; **33**(10):2202–10.

Boyle 2012
Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes art 3 and 5 years: population based cohort study. *BMJ* 2012;**344**:e896. [DOI: 10.1136/bmj.e896

Bujold 2014
Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. *Prenatal Diagnosis* 2014;**34**(7):642–8.

Churchill 2013
Churchill D, Duley L, Thornton JG, Jones L. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD003106.pub2

Davis 2007
Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L, et al. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. *Hypertension in Pregnancy* 2007;**26**(1):77–87.

De Regil 2011
De Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008873.pub2

Dietz 2012
Dietz PM, Rizzo JH, England LJ, Callaghan WM, Vesco KK, Bruce FC, et al. Early term delivery and health care utilization in the first year of life. *Journal of Pediatrics* 2012; **161**(2):234–9.

Dolea 2003
Dolea C, AbouZahr C. Global burden of hypertensive disorders of pregnancy in the year 2000. Evidence and Information for Policy (EIP), World Health Organization, Geneva, July 2003. www.who.int/healthinfo/statistics/bod_hypertensivedisordersofpregnancy.pdf (Accessed on December 12, 2012).

Duley 2009
Duley L, Henderson-Smart DJ, Walker GJA. Interventions for treating pre-eclampsia and its consequences: generic protocol. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD007756

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hofmeyr 2014
Hofmyer GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD001059.pub4

Hutcheon 2011
Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of

pregnancy. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2011;**25**(4):391–403.

Khan 2006
Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: systematic review. *Lancet* 2006;**367**(9516):1066–74.

Lowe 2014
Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. Guideline for the Management of Hypertensive Disorders of Pregnancy. Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) 2014.

Magee 2008
Magee LA, Helewa M, Moutquin JM, Von Dadelszen P, Hypertension Guideline Committee, Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRHS) Scholars. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Journal of Obstetrics and Gynaecology Canada: JOGC* 2008; **30**(3 Suppl):S1.

Magee 2014
Magee LA, Pels A, Helewa M, Rey E, Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health* 2014; 4(2):105–45.

Magloire 2012
Magloire L, Funai EF. Gestational hypertension. www.uptodate.com/contents/gestational-hypertension (accessed 10 March 2014).

Maslow 2000
Maslow AS, Sweeny AL. Elective induction of labor as a risk factor for cesarean delivery among low-risk women at term. *Obstetrics and Gynecology* 2000;**95**(6 Pt 1):917–22.

Meher 2005
Meher S, Duley L, Prevention of Pre-eclampsia Cochrane Review Authors. Interventions for preventing pre-eclampsia and its consequences: generic protocol. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD005301

NICE 2010
National Collaborating Centre for Women's and Children's Health. *Hypertension in Pregnancy: the Management of Hypertensive Disorders During Pregnancy. NICE Clinical Guideline 107*. London: National Institute for Health and Clinical Excellence, August 2010.

Norwitz 2013
Norwitz ER, Funai EF. Expectant management of severe preeclampsia. www.uptodate.com/contents/expectant-management-of-severe-preeclampsia (accessed 10 March 2014).

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Saftlas 1990
Saftlas AF, Olson DR, Franks AL, Atrash AK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. *American Journal of Obstetrics and Gynecology* 1990;**163**(2):460–5.

Sibai 2005
Sibai B, Dekker G, Kupferminc G. Pre-eclampsia. *Lancet* 2005;**365**(9461):785–99.

Spong 2011
Spong CY, Mercer BM, D'alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstetrics and Gynecology* 2011;**118**(2 Pt 1):323–33.

Steegers 2010
Steegers EAP, Van Dadelszen P, Pijnenbong R. Pre-eclampsia. *Lancet* 2010;**376**:631–44.

Tita 2009
Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *New England Journal of Medicine* 2009;**360**(2):111–20.

Villar 2003
Villar J, Say L, Gülmezoglu M, et al. Eclampsia and preeclampsia: a worldwide health problem for 2000 years. In: Critchley H, Maclean A, Poston L, Walker J editor (s). *Pre-eclampsia*. London, England: RCOG Press, 2003: 57–72.

Wang 2004
Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. *Pediatrics* 2004;**114**(2): 372–6.

WHO 2011
World Health Organization. *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*. Geneva: WHO, 2011.

Wilmink 2010
Wilmink FA, Hukkelhoven CW, Lunshof S, Mol BW, Van der Post JA, Papatsonis DN. Neonatal outcome following elective cesarean section beyond 37 weeks of gestation: a 7-year retrospective analysis of a national registry. *American Journal of Obstetrics and Gynecology* 2010;**202**(3):1–8.

References to other published versions of this review

Novikova 2011
Novikova N, Cluver C, Koopmans CM. Delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2011, Issue 8. [DOI: 10.1002/14651858.CD009273

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Broekhuijsen 2015

Methods	2-arm multicentre randomised controlled trial.
Participants	**Setting**: 51 hospitals in the Netherlands. June 2009 to March 2013. **Inclusion criteria**: pregnant women (singleton or multiple pregnancies), 34^{+0}-36^{+6} weeks' gestation, who had gestational hypertension, mild pre-eclampsia, or deteriorating chronic hypertension. Gestational hypertension: diastolic blood pressure ≥ 100 mmHg on 2 occasions at least 6 hours apart in a woman who was normotensive until at least 20 weeks GA. Mild PE: diastolic blood pressure > 90 mmHg on 2 occasions at least 6 hours apart in a woman who was normotensive until at least 20 weeks GA plus proteinuria (> 300 mg total protein in a 24-hour urine collection or > 30 in a spot urine protein:creatinine ratio). Chronic hypertension: diastolic blood pressure ≥ 90 mmHg on 2 occasions at least 6 hours apart, diagnosed before 20 weeks of gestation Women with singleton or multiple pregnancies are eligible, independent of the position of the fetus (i.e. cephalic or breech). Neither diabetes mellitus, nor small-for-gestational age nor a history of caesarean section are exclusion criteria **Exclusion criteria**: diastolic blood pressure ≥ 110 mmHg despite medication, systolic blood pressure ≥ 170 mmHg despite medication, proteinuria ≥ 5 g per 24 hours, eclampsia, HELLP syndrome, pulmonary oedema or cyanosis, oliguria < 500 mL in 24 hours, renal disease, heart disease, HIV-positive, non-reassuring fetal heart rate, absent flow or reversed flow in the umbilical artery, fetal abnormalities including an abnormal karyotype, ruptured membranes and severe pre-eclamptic complaints such as frontal headaches
Interventions	**Experimental intervention**: planned early delivery with an induction of labour started within 24 hours after randomisation If vaginal delivery was not contraindicated and the cervix was considered favourable an amniotomy was performed and augmentation with oxytocin was used if indicated. In cases of unfavourable cervix, induction was preceded with cervical ripening according to the local protocol. Prostaglandins were not administered to women with a history of caesarean section and in these cases a Foley catheter, followed by amniotomy and oxytocin were used instead Where vaginal delivery is contraindicated (e.g. breech presentation or a history of 2 caesarean sections) the woman will be delivered by caesarean section within 24 hours after randomisation. 353 women randomised (1 woman subsequently withdrew) **Control/Comparison intervention**: expectant monitoring until 37 weeks of GA. Monitored until the onset of spontaneous delivery. If labour had not started at 37 + 0 weeks, labour was induced. Monitoring consisted of the mother's assessment of fetal movements, electronic fetal heart rate monitoring at least twice a week and maternal blood pressure measurement and screening of urine for protein. Intervention was recommended if the fetal or maternal condition did not justify expectant monitoring any more, similar to the exclusion criteria of the trial. 351 women randomised
Outcomes	Composite adverse maternal outcome (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, placental abruption, and/or maternal death), neonatal

Broekhuijsen 2015 (*Continued*)

	morbidity, neonatal death
Funding source	This trial was funded by ZonMw, The Netherlands Organisation for Health Research and Development, programme Doelmatigheidsonderzoek (Health Care Efficiency Research, grant 171102012)
Declarations of interest	No conflicts of interests declared.
Notes	Registered with the Netherlands Trial Register (NTR1792) HW emailed Dr Koopmans on 6/8/15 to ask if the composite infant outcome by gestation at randomisation is available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done with a web-based system by random permuted blocks with variable block size (range 2 - 4), stratified by centre
Allocation concealment (selection bias)	Low risk	Central allocation of women concealed allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study: "it is impossible to blind the healthcare workers and patients involved for the strategy to which the woman is allocated"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment does not appear to have been blinded. Data were entered into a web-based case report form, coded to ensure confidentiality
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women are accounted for. 1 woman withdrew after being randomised to planned early delivery. Analysis was by intention-to-treat in Broekhuijsen 2014, but not in Broekhuijsen 2015. A subset of 200 women received quality-of-life questionnaires. The results of this subset of women are not included in this review
Selective reporting (reporting bias)	Low risk	All outcomes that were prespecified in the protocol were reported
Other bias	Low risk	The baseline characteristics of women randomly assigned to planned delivery and expectant monitoring appear to be similar.

Broekhuijsen 2015 (*Continued*)

		"When compared with randomly assigned women, women who declined to be randomly assigned more often finished higher education, were more often non-smokers, were more often nulliparous, and had a lower GA. Otherwise, baseline characteristics were much the same in randomly assigned and not randomly assigned women". This may affect the generalisability of the results of this study, but is not a source of bias per se

Hamed 2014

Methods	2-arm randomised controlled trial.
Participants	**Setting:** Saudi Arabia and Egypt. Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. April 2012 - October 2013 **Inclusion criteria**: women with a singleton pregnancy with mild to moderate essential chronic hypertension without proteinuria. GA at recruitment 24 - 36 weeks. Diastolic blood pressure between 90 and 110 mmHg and/or systolic pressure between 140 and 160 mmHg on 2 occasions at least 6 hours apart in the first half of pregnancy or if the woman was known to be hypertensive before pregnancy **Exclusion criteria**: severe chronic hypertension (blood pressure ≥ 160/110 mmHg); gestational hypertension; new onset pre-eclampsia in a previously normotensive woman; secondary hypertension (excluded by examination and relevant investigations such as kidney function tests, urine analysis, abdominal ultrasound, renal artery Doppler, urinary catecholamine, and autoimmune serologic profile); target organ damage excluded by opthalmological fundus examination, and renal and cardiac assessment; and medical or obstetric risk factors such as malpresentation at recruitment, placenta previa, uterine scar, fetal anomalies, or pregestational diabetes mellitus
Interventions	**Experimental intervention**: delivery at 37 completed weeks, provided that no maternal or fetal complications demanded elective preterm labour. If the Bishop score was > 8, labour was induced by oxytocin infusion and amniotomy. If the Bishop score was 8 or less, cervical ripening was induced by vaginal misoprostol at a dose of 50 µg every 6 hours up to a maximum of 200 µg, followed by an oxytocin infusion and amniotomy Women continued any antihypertensive drugs that they used before recruitment, and the dose was monitored to achieve control of blood pressure. 38 women were randomised **Control/Comparison intervention**: expectant management until the spontaneous onset of labour or 41 gestational weeks Monitored as outpatients for blood pressure measurement with dipstick screening for proteinuria 2 - 3 times per week. Hospitalised during the initial evaluation and if maternal or fetal complications developed Women continued any antihypertensive drugs that they used before recruitment, and the dose was monitored to achieve control of blood pressure. 38 women were randomised

Hamed 2014 (*Continued*)

Outcomes	Superimposed pre-eclampsia, severe hypertension, preterm delivery, placental abruption, oligohydramnios, intrauterine growth restriction, perinatal mortality, GA at delivery, birthweight, caesarean section, neonatal intensive care unit admission	
Funding source	The authors acknowledge the Deanship of Scientific Research in Qassim University for financial support for this work through an official grant (research number 1681/1433-1434)	
Declarations of interest	No conflicts of interests declared.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligible women were randomised by a computer-generated table, and allocated by 1:1 ratio to group A or group B
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible. This may have had an effect on other treatment decisions
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment does not appear to have been blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported on flow diagram
Selective reporting (reporting bias)	Unclear risk	Reporting appeared to be good; however no protocol was available to assess whether all prespecified outcomes were reported
Other bias	Low risk	The groups appear to be comparable at baseline

Koopmans 2009

Methods	2-arm multicentre randomised controlled trial
Participants	**Setting**: 38 hospitals (6 academic and 32 non-academic) in Netherlands between October 2005 and March 2008 **Inclusion criteria:** women with a singleton pregnancy at 36 (0 days) - 41 weeks (0 days) gestation who had gestational hypertension or mild pre-eclampsia. Gestational hypertension was defined as diastolic blood pressure of 95 mmHg or higher measured

Koopmans 2009 (*Continued*)

	on 2 occasions at least 6 hours apart. Mild pre-eclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on 2 occasions at least 6 hours apart, combined with proteinuria (2 or more occurrences of protein on a dipstick, > 300 mg total protein within a 24-hour urine collection, or ratio of protein to creatinine > 30 mg/mmol) **Exclusion criteria**: severe gestational hypertension or severe pre-eclampsia, defined as systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5 g or higher per 24 hours. Other exclusion criteria: pre-existing hypertension treated with antihypertensive drugs, diabetes mellitus, gestational diabetes needing insulin treatment, renal disease, heart disease, previous caesarean section, HELLP syndrome, oliguria of less than 500 mL per 24 hours, pulmonary oedema or cyanosis, HIV seropositivity, use of intravenous antihypertensive drugs, fetal anomalies, suspected intrauterine growth restriction, abnormalities detected during fetal-heart-rate monitoring, non-vertex position	
Interventions	**Experimental intervention**: induction of labour within 24 hours of randomisation. If the Bishop score was > 6, labour was induced with amniotomy and if needed augmentation with oxytocin. If the Bishop score was ≤ 6, cervical ripening was stimulated with intracervical or intravaginal prostaglandins or a balloon catheter. Use of oxytocin or prostaglandins depended on local protocols. 377 women randomised **Control/Comparison intervention**: expectant monitoring. They were monitored until the onset of spontaneous delivery, in hospital or outpatient setting, depending on the condition of the woman with frequent blood pressure measurements and testing of urine for protein of the mother. Fetal monitoring included movements as reported by the mother, electronic fetal-heart-rate monitoring and ultrasound examination. Induction of labour was recommended if the systolic blood pressure was 170 mmHG or higher or if the diastolic blood pressure was 110 mmHg or higher, if there was proteinuria of 5 g or higher per 24 hours, if eclampsia developed, if HELLP syndrome was present, if there was suspected fetal distress, if prelabour rupture of membranes lasting more than 48 hours occurred, if there was meconium-stained amniotic fluid, or a fetus with GA beyond 41 weeks. 379 women randomised	
Outcomes	Composite of poor maternal outcome which included maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, and placental abruption), progression to severe hypertension or proteinuria and a major postpartum haemorrhage (> 1000 mL blood loss)	
Funding source	This trial was funded by ZonMw, the Netherlands organisation for health research and development, programme Doelmatigheidsonderzoek (grant number 945-06-553)	
Declarations of interest	No conflicts of interests declared.	
Notes	HW emailed Dr Koopmans on 6/8/15 to ask if the mean and standard deviation are available for continuous variables (e.g. duration of hospital stay after delivery, economic outcomes), reported in publications as median and IQR. Also, whether health-related quality of life measures are available in a form that could be used in the review	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Koopmans 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Good random sequence generation. Block randomisation with a variable block size of 2 - 8. Web-based application used to stratify for centre, parity, and hypertensive-related disease (gestational hypertension or pre-eclampsia). Women were randomly allocated in a 1:1 ratio to receive either induction of labour or expectant monitoring
Allocation concealment (selection bias)	Low risk	Central allocation using a web-based application.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"in this open-label trial, masking of participants, obstetricians and outcome assessors was not possible for allocation of the randomisation number or intervention."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"in this open-label trial, masking of participants, obstetricians and outcome assessors was not possible for allocation of the randomisation number or intervention."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The analysis was by intention-to-treat. Data are reported for all randomised women Fewer women participated in the quality of life study (questionnaires were not available for 217 women. 48/539 did not respond to the questionnaire, giving a 91% response rate)
Selective reporting (reporting bias)	Low risk	All outcomes that were prespecified in the protocol were reported
Other bias	Low risk	The groups appear to be comparable at baseline. The report states that the funder "had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication"

Majeed 2014

Methods	2-arm randomised controlled trial.
Participants	**Setting**: May 2011 to April 2012 in Government Medical College, Kolkata, India **Inclusion criteria**: pregnant women at 36 - 40 weeks' gestation, with mild pre-eclampsia/gestational hypertension without proteinuria. A diagnosis of gestational hypertension

Majeed 2014 (*Continued*)

	was made if systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg for the first time during pregnancy without proteinuria. A diagnosis of mild pre-eclampsia was made if systolic blood pressure was 140 - 159 mmHg and diastolic blood pressure is 90 - 109 mmHg accompanied by proteinuria of > 0.3 g to < 5 g/24 hours **Exclusion criteria**: not described
Interventions	**Experimental intervention**: induction of labour (no further information) **Control/Comparison intervention**: expectant management (no further information) 100 women were randomised. The number of women in each group is not stated, so we assume it was 50, as women were randomised in a 1:1 manner
Outcomes	Maternal: severe hypertension, severe proteinuria, eclampsia, placental abruption, HELLP syndrome, disseminated intravascular coagulation, postpartum haemorrhage, retinal haemorrhage, pulmonary oedema. Caesarean section. Admission to delivery interval. Hospital stay. Perinatal: asphyxia, respiratory distress syndrome, very low birthweight, meconium aspiration, mechanical ventilation, neonatal intensive care unit admission
Funding source	No information given - abstract only.
Declarations of interest	No information given - abstract only.
Notes	This trial report was in abstract form only (which could explain the paucity of detail) HW emailed Professor Singh on 30/4/15 and 5/8/15, asking: How many women were recruited to each group? Please would you describe the process of randomisation and group allocation Would you be able to provide data on any of the following outcomes (review outcomes listed) No reply received at present.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States that women were "randomized in 1:1 manner", but no information on the method
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants and personnel to whether they had been assigned to induction of labour or expectant management
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned

Majeed 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of women allocated to each group is not reported, so it is not possible to assess whether data for all women have been reported
Selective reporting (reporting bias)	High risk	Only outcomes with significant differences between groups were reported
Other bias	Low risk	The report states that the groups were comparable at baseline

Owens 2014

Methods	2-arm randomised control trial.
Participants	**Setting**: women admitted to The Wiser Hospital for Women and Infants at the University of Mississippi Medical Center (UMMC) from March 2002 to June 2009 **Inclusion criteria**: pregnant women with mild pre-eclampsia, 34 - 37 weeks (with estimated fetal weight > 2000 g), no other maternal-fetal-pregnancy complications. (ACOG 2002 criteria for mild pre-eclampsia.) No maternal or fetal contraindications to conservative management. Age 18 - 50 **Exclusion criteria**: non-gestational diabetes, chronic hypertension, severe pre-eclampsia, non-reassuring fetal assessment intrauterine growth restriction fetal anomalies, multiple gestation, premature preterm rupture of membranes, placenta previa, unexplained vaginal bleeding, antihypertensive use, current gestation poor dating, contraindication to conservative management, active labour at admission
Interventions	**Experimental intervention**: planned early delivery via induction of labour or caesarean delivery within 12 hours of randomisation All study participants were treated with magnesium sulphate prophylaxis intrapartum and immediately postpartum 97 women were randomised, 3 were subsequently excluded for not meeting the inclusion criteria **Control/Comparison intervention**: inpatient expectant management, to 37 weeks' gestation unless there was spontaneous onset of labour or rupture of membranes, suspected placental abruption, development of severe PE of fetal compromise. All study participants were treated with magnesium sulphate prophylaxis intrapartum and immediately postpartum 86 women were randomised (11 were subsequently excluded for not meeting the inclusion criteria (7), voluntarily withdrawing from the study (1), and leaving the hospital (3))
Outcomes	Primary: maternal morbidity, mortality, and development of severe pre-eclampsia. Secondary: major neonatal morbidities and mortality
Funding source	Funded by Division of Maternal-fetal Medicine in the Department of Obstetrics and Gynaecology, University of Mississippi Medical Centre
Declarations of interest	No conflicts of interests declared.

Owens 2014 (*Continued*)

Notes	*ClinicalTrials.gov: NCT00789919* HW emailed Professor Owens on 11/8/15, asking how the random sequence was generated, if composite maternal and infant outcomes were available, and for duration of infant stay after delivery. No response was received	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised using stratified and random permuted blocks of 2 in consecutively numbered opaque envelopes. However, the sequence generation was not described
Allocation concealment (selection bias)	Low risk	Opaque envelopes concealed allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants and personnel to whether they had been assigned to induction of labour or expectant management
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The analysis was not intention-to-treat. 3 (out of 97) participants left the planned early delivery group, and 11 (out of 86) left the expectant management group, and were excluded from the analyses
Selective reporting (reporting bias)	Low risk	The outcomes prespecified in the protocol were reported
Other bias	Unclear risk	The study was stopped early, at 74% of the enrolment target, when hospital policy changed to discourage inpatient hospitalisation for "uncomplicated mild preterm preeclampsia". This left the study underpowered to demonstrate statistically significant differences

GA gestational age
HELLP: haemolysis, elevated liver enzymes and low platelet count
IQR: interquartile range
PE: pre-eclampsia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ramrakhyani 2001	Not a randomised controlled trial. No randomisation. Group allocation based on gestational age at presentation
Tukur 2007	Comparing planned early delivery by caesarean section with planned early delivery by induction with vaginal misoprostol

Characteristics of ongoing studies *[ordered by study ID]*

Shennan 2013

Trial name or title	PHOENIX - Pre-eclampsia in HOspital: Early iNductIon or eXpectant management
Methods	2-arm trial. "randomly allocated", no description of method of randomisation in trial registration
Participants	Pregnant women with pre-eclampsia between 34 and 37 weeks of gestation
Interventions	Experimental intervention: planned early birth. Induced within 48 hours of group allocation Control/Comparison intervention: monitored in hospital. Inpatient until 37 weeks then induced
Outcomes	Maternal morbidity, perinatal mortality, neurodevelopmental assessment at age 2
Starting date	April 2014. Anticipated to take approximately 3 years to recruit 900 women
Contact information	Professor Andrew Shennan (andrew.shennan@kcl.ac.uk)
Notes	ISRCTN01879376

DATA AND ANALYSES

Comparison 1. Planned early delivery versus expectant management (all women)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite maternal mortality and morbidity	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.57, 0.83]
2 Composite infant mortality and morbidity	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Maternal mortality	2	1457	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Eclampsia	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.14]
5 Pulmonary oedema	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.17]
6 Severe renal impairment	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.14, 0.92]
7 HELLP syndrome	3	1628	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.17, 0.93]
8 Thromboembolic disease	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.22, 12.58]
9 Abruptio placentae	3	1535	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.17, 2.34]
10 Postpartum haemorrhage	1	741	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.57, 1.35]
11 Severe hypertension	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12 Caesarean section	4	1728	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.07]
13 Assisted delivery (ventouse/forceps)	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.70, 1.24]
14 Maternal morbidity of caesarean section	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.35]
14.1 Endometritis	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.35]
15 Maternal morbidity related to induction of labour	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Uterine rupture	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Admission to a high care or intensive care unit	1	708	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.16, 1.07]
17 Fetal death	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Neonatal death	3	1535	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.14]
19 Grade III or IV intraventricular or intracerebral haemorrhage	1	674	Risk Ratio (M-H, Fixed, 95% CI)	6.92 [0.36, 133.41]
20 Nectrotising enterocolitis	2	1338	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.89]
21 Respiratory distress syndrome	3	1511	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.20, 4.18]
22 Small-for-gestational age	3	1001	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.89, 2.79]
23 Neonatal seizures	1	699	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [0.45, 35.30]
24 Apgar score less than seven at five minutes	2	1454	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.60, 2.05]
25 Cord blood pH less than 7.1 or as defined by trial authors	2	1145	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.09]
26 Surfactant use	1	639	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Neonatal intensive care unit or high care unit admission	4	1585	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.13, 2.40]
28 Early neonatal sepsis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29 Duration of hospital stay after delivery for mother (days)	2	925	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.46, 0.15]

30 Duration of hospital stay after delivery for baby (days)	1	756	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.57, 0.17]

Comparison 2. Planned early delivery versus expectant management (by gestational age)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite maternal mortality and morbidity	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.57, 0.83]
1.1 34 + 0 to 36 + 6 weeks GA at randomisation	2	778	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.48, 1.24]
1.2 37 + 0 to 38 + 6 weeks GA at randomisation	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.90]
1.3 39 + 0 to 41 + 0 weeks GA at randomisation	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.88]
2 Respiratory distress syndrome	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.16, 5.55]
2.1 34 + 0 to 36 + 6 weeks GA at randomisation	2	778	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [1.35, 8.18]
2.2 37 + 0 to 38 + 6 weeks GA at randomisation	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.72]
2.3 39 + 0 to 41 + 0 weeks GA at randomisation	1	301	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.07, 17.74]
3 Composite infant mortality and morbidity	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.46, 1.28]
3.1 36 + 0 to 36 + 6 weeks GA at randomisation	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.29, 24.10]
3.2 37 + 0 to 38 + 6 weeks GA at randomisation	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.31, 1.49]
3.3 39 + 0 to 41 + 0 weeks GA at randomisation	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.49]

Comparison 3. Planned early delivery versus expectant management (by each gestational week)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite maternal mortality and morbidity	2	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.57, 0.83]
1.1 34 + 0 to 34 + 6 weeks GA at randomisation	1	154	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [0.23, 97.34]
1.2 35 + 0 to 35 + 6 weeks GA at randomisation	1	236	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.10]
1.3 36 + 0 to 36 + 6 weeks GA at randomisation	2	388	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.59, 1.62]

1.4 37 + 0 to 37 + 6 weeks GA at randomisation	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.52, 1.08]
1.5 38 + 0 to 38 + 6 weeks GA at randomisation	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.43, 0.94]
1.6 39 + 0 to 39 + 6 weeks GA at randomisation	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.14]
1.7 40 + 0 to 41 + 0 weeks GA at randomisation	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.26, 0.79]
2 Respiratory distress syndrome	1	703	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [1.38, 8.01]
2.1 34 + 0 to 34 + 6 weeks GA at randomisation	1	154	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.78, 7.24]
2.2 35 + 0 to 35 + 6 weeks GA at randomisation	1	236	Risk Ratio (M-H, Fixed, 95% CI)	7.62 [0.93, 62.27]
2.3 36 + 0 to 36 + 6 weeks GA at randomisation	1	313	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [0.39, 30.15]
3 Composite infant mortality and morbidity	1	756	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.46, 1.29]
3.1 36 + 0 to 36 + 6 weeks GA at randomisation	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.29, 24.10]
3.2 37 + 0 to 37 + 6 weeks GA at randomisation	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.17, 1.35]
3.3 38 + 0 to 38 + 6 weeks GA at randomisation	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.33, 4.24]
3.4 39 + 0 to 39 + 6 weeks GA at randomisation	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.32, 1.95]
3.5 40 + 0 to 41 + 0 weeks GA at randomisation	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.19, 2.12]

Comparison 4. Planned early delivery versus expectant management (by condition)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite maternal mortality and morbidity	2	1445	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.58, 0.85]
1.1 Gestational hypertension	2	678	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 1.00]
1.2 Mild pre-eclampsia	2	570	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.45, 0.81]
1.3 Chronic hypertension	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.10, 2.86]
2 Respiratory distress syndrome	1	703	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [1.36, 8.31]
2.1 Gestational hypertension	1	182	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [0.45, 34.34]
2.2 Mild pre-eclampsia	1	324	Risk Ratio (M-H, Fixed, 95% CI)	4.82 [1.07, 21.65]
2.3 Chronic hypertension	1	197	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.55, 8.35]

Analysis 1.1. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 1 Composite maternal mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 1 Composite maternal mortality and morbidity

Study or subgroup	Delivery n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	4/352	11/351		6.2 %	0.36 [0.12, 1.13]
Koopmans 2009	117/377	166/379		93.8 %	0.71 [0.59, 0.86]
Total (95% CI)	**729**	**730**		**100.0 %**	**0.69 [0.57, 0.83]**

Total events: 121 (Delivery), 177 (Expectant)
Heterogeneity: $Chi^2 = 1.32$, df = 1 (P = 0.25); I^2 =24%
Test for overall effect: Z = 3.94 (P = 0.000083)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 2 Composite infant mortality and morbidity.

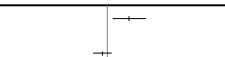
Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 2 Composite infant mortality and morbidity

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Broekhuijsen 2015	20/352	6/351			3.32 [1.35, 8.18]
Koopmans 2009	24/377	32/379			0.75 [0.45, 1.26]

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 3 Maternal mortality.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 3 Maternal mortality

Study or subgroup	Delivery n/N	Expectant Manage-ment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	0/352	0/351			Not estimable
Koopmans 2009	0/377	0/377			Not estimable
Total (95% CI)	**729**	**728**			**Not estimable**
Total events: 0 (Delivery), 0 (Expectant Management)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 4 Eclampsia.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 4 Eclampsia

Study or subgroup	Delivery n/N	Expectant manage-ment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	0/352	2/351		100.0 %	0.20 [0.01, 4.14]
Koopmans 2009	0/377	0/379			Not estimable
Total (95% CI)	**729**	**730**		**100.0 %**	**0.20 [0.01, 4.14]**

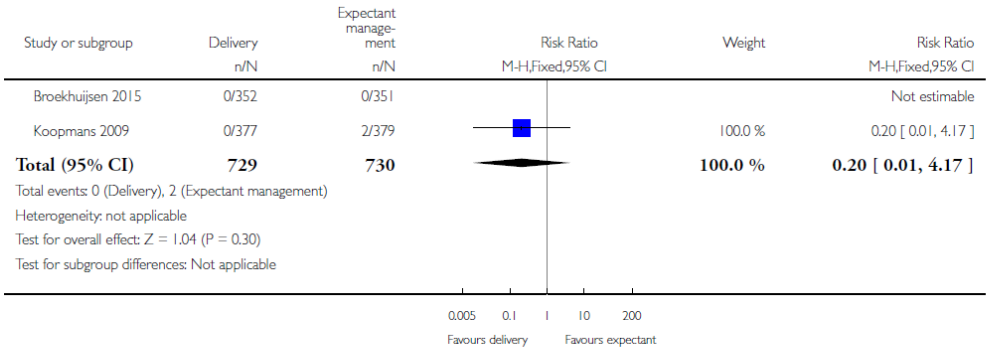
Total events: 0 (Delivery), 2 (Expectant management)
Heterogeneity: not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 5 Pulmonary oedema.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 5 Pulmonary oedema



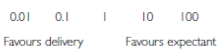
Analysis 1.6. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 6 Severe renal impairment.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 6 Severe renal impairment

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Majeed 2014 (1)	5/50	14/50		100.0 %	0.36 [0.14, 0.92]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.36 [0.14, 0.92]**
Total events: 5 (Delivery), 14 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.032)					
Test for subgroup differences: Not applicable					



(1) Acute renal failure

Analysis 1.7. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 7 HELLP syndrome.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 7 HELLP syndrome

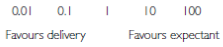
Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	3/352	6/351		32.2 %	0.50 [0.13, 1.98]
Koopmans 2009	4/377	11/379		58.8 %	0.37 [0.12, 1.14]
Owens 2014	0/94	1/75		8.9 %	0.27 [0.01, 6.45]
Total (95% CI)	**823**	**805**		**100.0 %**	**0.40 [0.17, 0.93]**

Total events: 7 (Delivery), 18 (Expectant management)

Heterogeneity: $Chi^2 = 0.18$, $df = 2$ ($P = 0.91$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.14$ ($P = 0.033$)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 8 Thromboembolic disease.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 8 Thromboembolic disease

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	1/352	1/351		66.8 %	1.00 [0.06, 15.88]
Koopmans 2009	1/377	0/379		33.2 %	3.02 [0.12, 73.80]
Total (95% CI)	**729**	**730**		**100.0 %**	**1.67 [0.22, 12.58]**

Total events: 2 (Delivery), 1 (Expectant management)
Heterogeneity: $Chi^2 = 0.26$, $df = 1$ ($P = 0.61$); $I^2 = 0.0\%$
Test for overall effect: $Z = 0.50$ ($P = 0.62$)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 9 Abruptio placentae.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 9 Abruptio placentae

Study or subgroup	Delivery n/N	Expectant manage-ment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	0/352	2/351		45.5 %	0.20 [0.01, 4.14]
Hamed 2014	3/38	3/38		54.5 %	1.00 [0.22, 4.65]
Koopmans 2009	0/377	0/379			Not estimable
Total (95% CI)	**767**	**768**		**100.0 %**	**0.64 [0.17, 2.34]**

Total events: 3 (Delivery), 5 (Expectant management)

Heterogeneity: $Chi^2 = 0.90$, df = 1 (P = 0.34); I^2 =0.0%

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 10 Postpartum haemorrhage.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 10 Postpartum haemorrhage

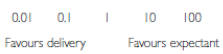
Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Koopmans 2009	35/370	40/371		100.0 %	0.88 [0.57, 1.35]
Total (95% CI)	**370**	**371**		**100.0 %**	**0.88 [0.57, 1.35]**

Total events: 35 (Delivery), 40 (Expectant management)

Heterogeneity: not applicable

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 11 Severe hypertension.

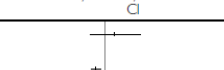
Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 11 Severe hypertension

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hamed 2014 (1)	5/38	3/38			1.67 [0.43, 6.49]
Koopmans 2009 (2)	62/373	103/377			0.61 [0.46, 0.81]
Owens 2014 (3)	3/94	20/75			0.12 [0.04, 0.39]

Test for subgroup differences: Not applicable



(1) blood pressure >=160/110mm Hg

(2) diastolic blood pressure >110mm Hg

(3) systolic >160mm Hg or diastolic >110mm Hg on two occasions at least 4 hours apart

Analysis 1.12. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 12 Caesarean section.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 12 Caesarean section

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	107/352	114/351		49.4 %	0.94 [0.75, 1.16]
Koopmans 2009	54/377	72/379		31.1 %	0.75 [0.55, 1.04]
Majeed 2014	12/50	14/50		6.1 %	0.86 [0.44, 1.66]
Owens 2014	42/94	28/75		13.5 %	1.20 [0.83, 1.73]
Total (95% CI)	**873**	**855**		**100.0 %**	**0.91 [0.78, 1.07]**

Total events: 215 (Delivery), 228 (Expectant management)

Heterogeneity: $Chi^2 = 3.51$, $df = 3$ ($P = 0.32$); $I^2 = 15\%$

Test for overall effect: $Z = 1.17$ ($P = 0.24$)

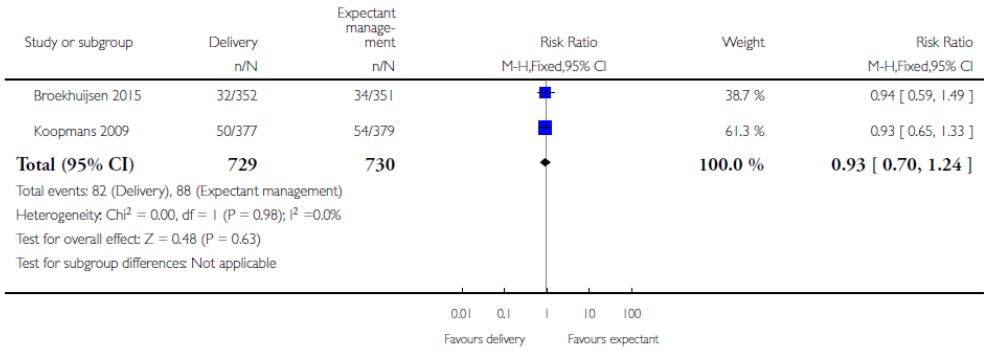
Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 13 Assisted delivery (ventouse/forceps).

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 13 Assisted delivery (ventouse/forceps)



Analysis 1.14. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 14 Maternal morbidity of caesarean section.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 14 Maternal morbidity of caesarean section

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Endometritis					
Koopmans 2009	3/377	4/379		100.0 %	0.75 [0.17, 3.35]
Total (95% CI)	**377**	**379**		**100.0 %**	**0.75 [0.17, 3.35]**
Total events: 3 (Delivery), 4 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
Test for subgroup differences: Not applicable					

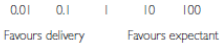
Analysis 1.15. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 15 Maternal morbidity related to induction of labour.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 15 Maternal morbidity related to induction of labour

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Uterine rupture					
Koopmans 2009	0/377	0/379			Not estimable
Total (95% CI)	**377**	**379**			**Not estimable**
Total events: 0 (Delivery), 0 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					



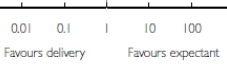
Analysis 1.16. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 16 Admission to a high care or intensive care unit.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 16 Admission to a high care or intensive care unit

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Koopmans 2009	6/360	14/348		100.0 %	0.41 [0.16, 1.07]
Total (95% CI)	**360**	**348**		**100.0 %**	**0.41 [0.16, 1.07]**
Total events: 6 (Delivery), 14 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.83 (P = 0.068)					
Test for subgroup differences: Not applicable					



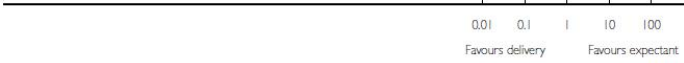
Analysis 1.17. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 17 Fetal death.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 17 Fetal death

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Koopmans 2009	0/377	0/379			Not estimable
Total (95% CI)	**377**	**379**			**Not estimable**
Total events: 0 (Delivery), 0 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 1.18. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 18 Neonatal death.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 18 Neonatal death

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015	0/352	0/351			Not estimable
Hamed 2014 (1)	2/38	1/38		100.0 %	2.00 [0.19, 21.14]
Koopmans 2009	0/377	0/379			Not estimable
Total (95% CI)	**767**	**768**		**100.0 %**	**2.00 [0.19, 21.14]**

Total events: 2 (Delivery), 1 (Expectant management)
Heterogeneity: not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable

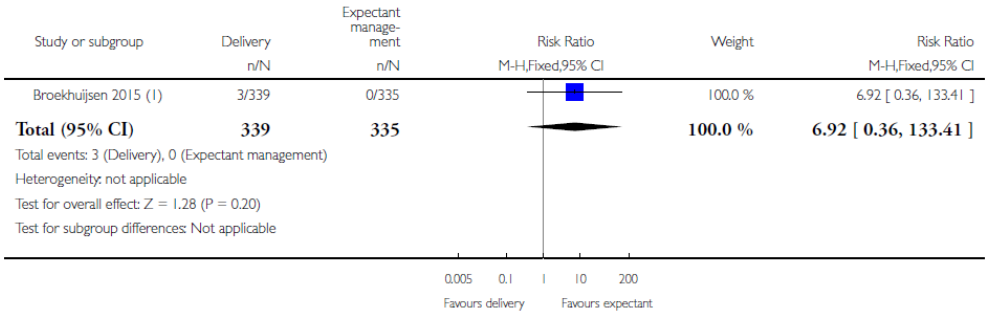
(1) after 24 weeks up until the first week of life

Analysis 1.19. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 19 Grade III or IV intraventricular or intracerebral haemorrhage.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 19 Grade III or IV intraventricular or intracerebral haemorrhage



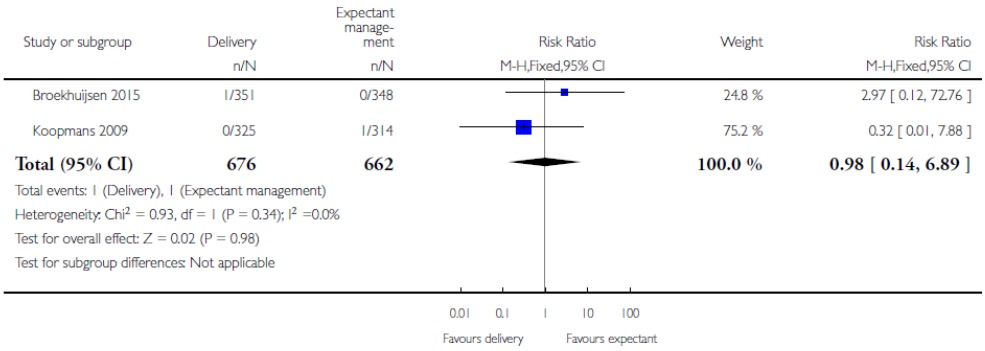
(1) intraventricular haemorrhage

Analysis 1.20. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 20 Necrotising enterocolitis.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 20 Necrotising enterocolitis

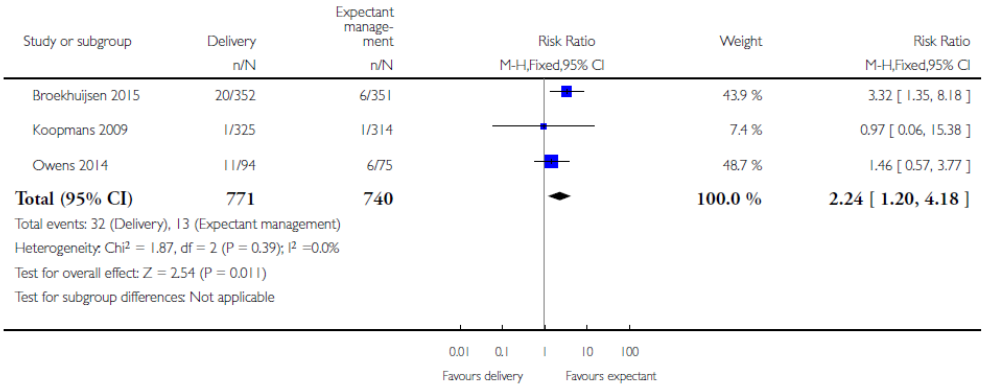


Analysis 1.21. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 21 Respiratory distress syndrome.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 21 Respiratory distress syndrome



Analysis 1.22. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 22 Small-for-gestational age.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 22 Small-for-gestational age

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hamed 2014 (1)	6/38	4/38		23.9 %	1.50 [0.46, 4.89]
Koopmans 2009 (2)	3/377	0/379		3.0 %	7.04 [0.36, 135.77]
Owens 2014	19/94	11/75		73.1 %	1.38 [0.70, 2.71]
Total (95% CI)	**509**	**492**		**100.0 %**	**1.58 [0.89, 2.79]**
Total events: 28 (Delivery), 15 (Expectant management)					
Heterogeneity: $Chi^2 = 1.14$, df = 2 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.56 (P = 0.12)					
Test for subgroup differences: Not applicable					

(1) IUGR: estimated fetal weight below the 10th percentile according to population-based growth curves, coupled with abnormally high doppler indices

(2) low birthweight

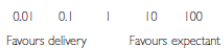
Analysis 1.23. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 23 Neonatal seizures.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 23 Neonatal seizures

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015 (1)	4/351	1/348		100.0 %	3.97 [0.45, 35.30]
Total (95% CI)	**351**	**348**		**100.0 %**	**3.97 [0.45, 35.30]**
Total events: 4 (Delivery), 1 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.22)					
Test for subgroup differences: Not applicable					



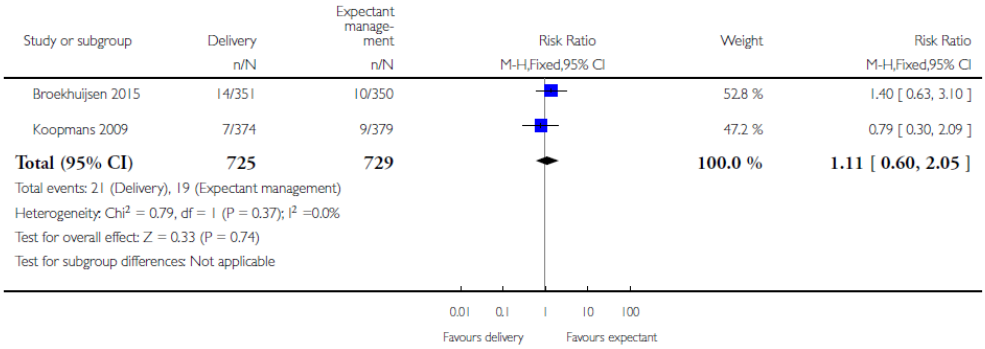
(1) "convulsions"

Analysis 1.24. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 24 Apgar score less than seven at five minutes.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 24 Apgar score less than seven at five minutes

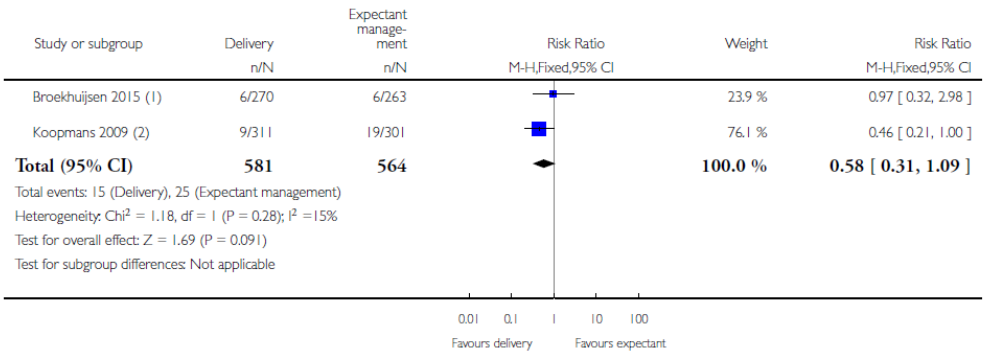


Analysis 1.25. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 25 Cord blood pH less than 7.1 or as defined by trial authors.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 25 Cord blood pH less than 7.1 or as defined by trial authors



(1) less than 7.05

(2) less than 7.05

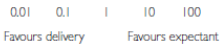
Analysis 1.26. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 26 Surfactant use.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 26 Surfactant use

Study or subgroup	Delivery n/N	Expectant manage-ment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Koopmans 2009	0/325	0/314			Not estimable
Total (95% CI)	**325**	**314**			**Not estimable**
Total events: 0 (Delivery), 0 (Expectant management)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

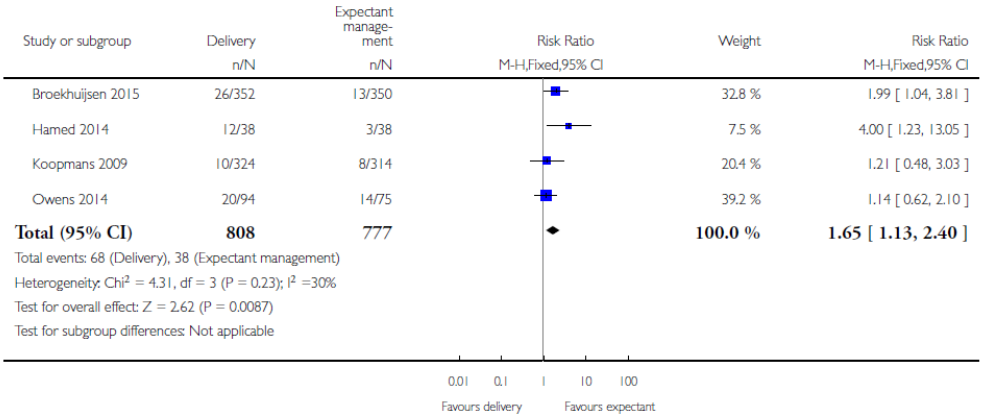


Analysis 1.27. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 27 Neonatal intensive care unit or high care unit admission.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 27 Neonatal intensive care unit or high care unit admission



Analysis 1.28. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 28 Early neonatal sepsis.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 28 Early neonatal sepsis

Study or subgroup	Delivery n/N	Expectant management n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Broekhuijsen 2015 (1)	36/351	22/348			1.62 [0.97, 2.70]
Koopmans 2009	0/377	1/379			0.34 [0.01, 8.20]
Test for subgroup differences: Not applicable					

(1) suspected or confirmed infection or sepsis

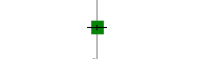
Analysis 1.29. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 29 Duration of hospital stay after delivery for mother (days).

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 29 Duration of hospital stay after delivery for mother (days)

Study or subgroup	Delivery N	Mean(SD)	Expectant N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Koopmans 2009	377	1.6 (1.8)	379	1.9 (3.9)		50.3 %	-0.30 [-0.73, 0.13]
Owens 2014 (1)	94	3.1 (1.26)	75	3.11 (1.56)		49.7 %	-0.01 [-0.45, 0.43]
Total (95% CI)	**471**		**454**			**100.0 %**	**-0.16 [-0.46, 0.15]**
Heterogeneity: Chi^2 = 0.86, df = 1 (P = 0.35); I^2 =0.0%							
Test for overall effect: Z = 1.00 (P = 0.32)							
Test for subgroup differences: Not applicable							



(1) SD calculated from SE

Analysis 1.30. Comparison 1 Planned early delivery versus expectant management (all women), Outcome 30 Duration of hospital stay after delivery for baby (days).

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 1 Planned early delivery versus expectant management (all women)

Outcome: 30 Duration of hospital stay after delivery for baby (days)

Study or subgroup	Delivery N	Mean(SD)	Expectant N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Koopmans 2009	377	2.5 (2.4)	379	2.7 (2.8)		100.0 %	-0.20 [-0.57, 0.17]
Total (95% CI)	**377**		**379**			**100.0 %**	**-0.20 [-0.57, 0.17]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable

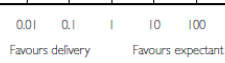
Analysis 2.1. Comparison 2 Planned early delivery versus expectant management (by gestational age), Outcome 1 Composite maternal mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 2 Planned early delivery versus expectant management (by gestational age)

Outcome: 1 Composite maternal mortality and morbidity

Study or subgroup	Delivery n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 34 + 0 to 36 + 6 weeks GA at randomisation					
Broekhuijsen 2015	4/352	11/351		6.3 %	0.36 [0.12, 1.13]
Koopmans 2009	18/40	15/35		9.1 %	1.05 [0.63, 1.75]
Subtotal (95% CI)	**392**	**386**		**15.3 %**	**0.77 [0.48, 1.24]**
Total events: 22 (Delivery), 26 (Expectant)					
Heterogeneity: Chi^2 = 3.09, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 37 + 0 to 38 + 6 weeks GA at randomisation					
Koopmans 2009	59/195	81/185		47.2 %	0.69 [0.53, 0.90]
Subtotal (95% CI)	**195**	**185**		**47.2 %**	**0.69 [0.53, 0.90]**
Total events: 59 (Delivery), 81 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.70 (P = 0.0070)					
3 39 + 0 to 41 + 0 weeks GA at randomisation					
Koopmans 2009	40/142	70/159		37.5 %	0.64 [0.47, 0.88]
Subtotal (95% CI)	**142**	**159**		**37.5 %**	**0.64 [0.47, 0.88]**
Total events: 40 (Delivery), 70 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.77 (P = 0.0056)					
Total (95% CI)	**729**	**730**		**100.0 %**	**0.68 [0.57, 0.83]**
Total events: 121 (Delivery), 177 (Expectant)					
Heterogeneity: Chi^2 = 4.06, df = 3 (P = 0.26); I^2 =26%					
Test for overall effect: Z = 3.96 (P = 0.000074)					
Test for subgroup differences: Chi^2 = 0.41, df = 2 (P = 0.81), I^2 =0.0%					

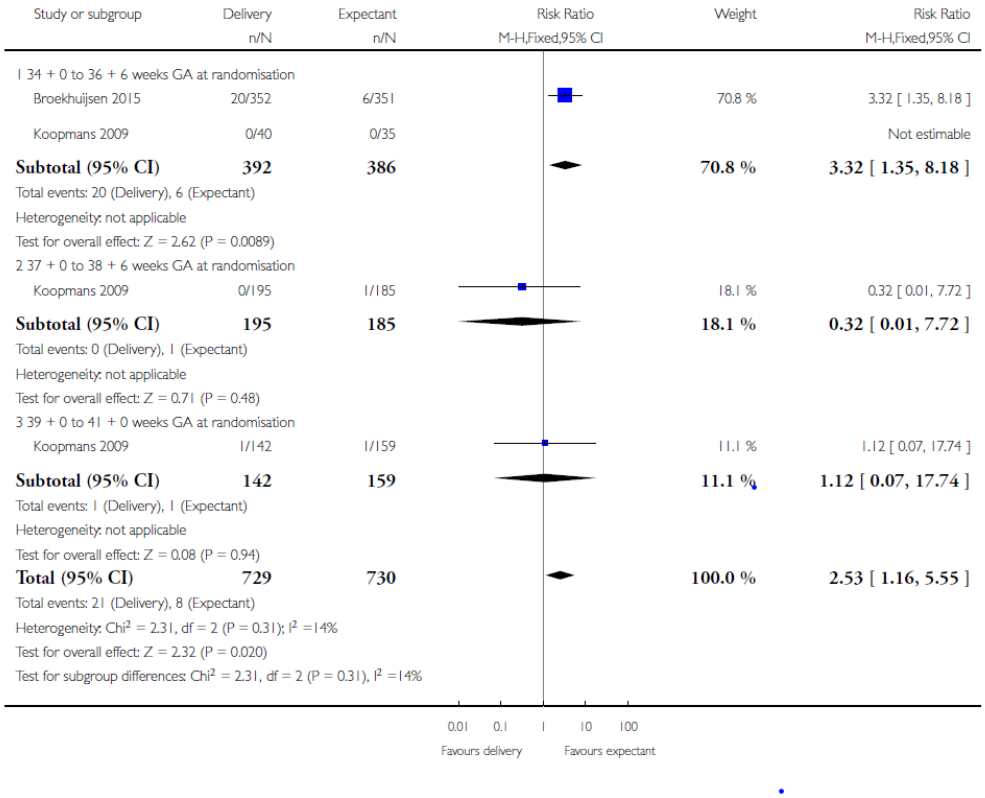


Analysis 2.2. Comparison 2 Planned early delivery versus expectant management (by gestational age), Outcome 2 Respiratory distress syndrome.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 2 Planned early delivery versus expectant management (by gestational age)

Outcome: 2 Respiratory distress syndrome

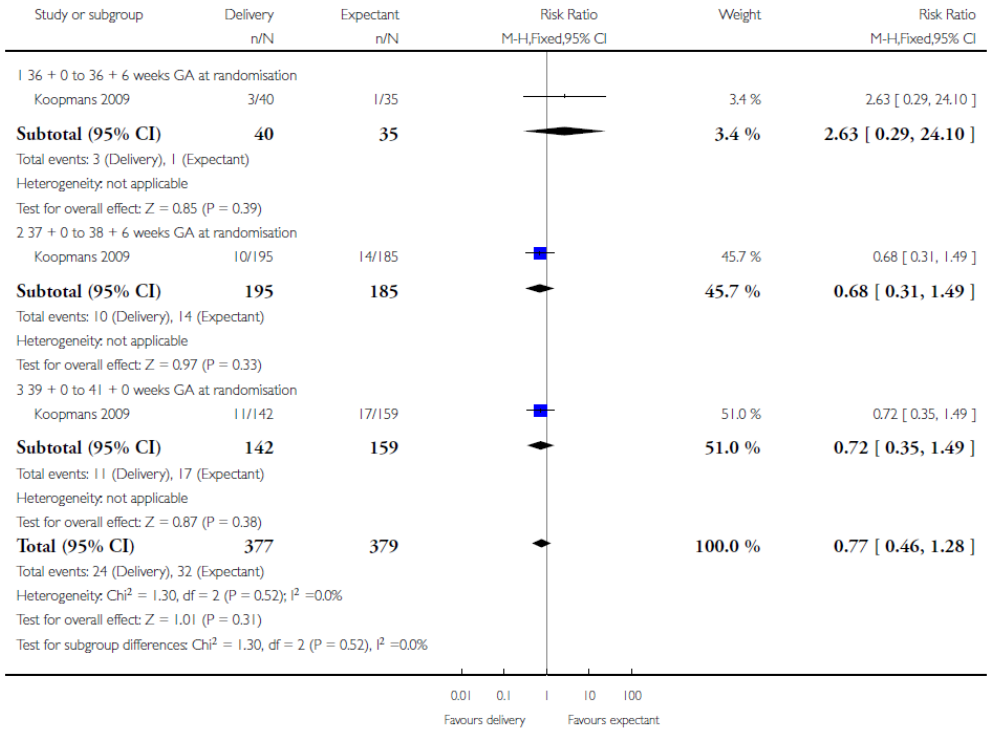


Analysis 2.3. Comparison 2 Planned early delivery versus expectant management (by gestational age), Outcome 3 Composite infant mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 2 Planned early delivery versus expectant management (by gestational age)

Outcome: 3 Composite infant mortality and morbidity

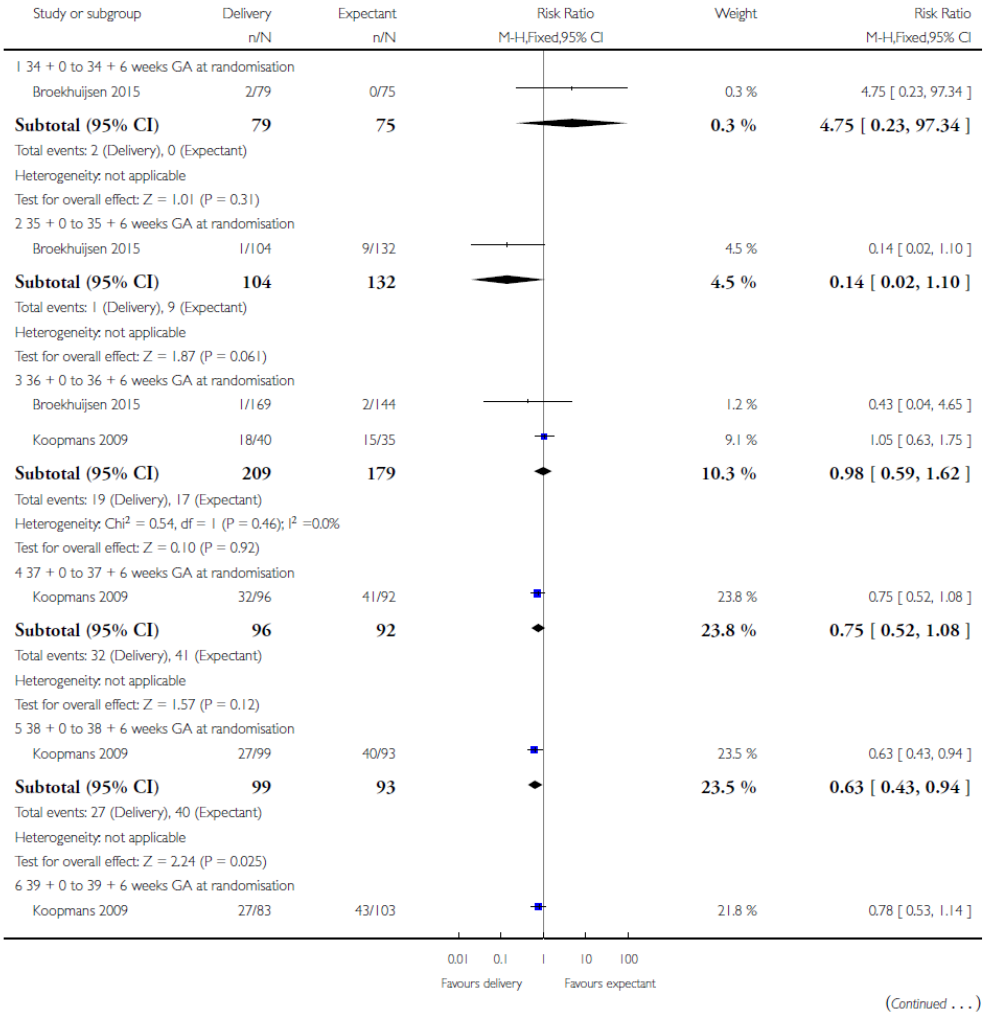


Analysis 3.1. Comparison 3 Planned early delivery versus expectant management (by each gestational week), Outcome 1 Composite maternal mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

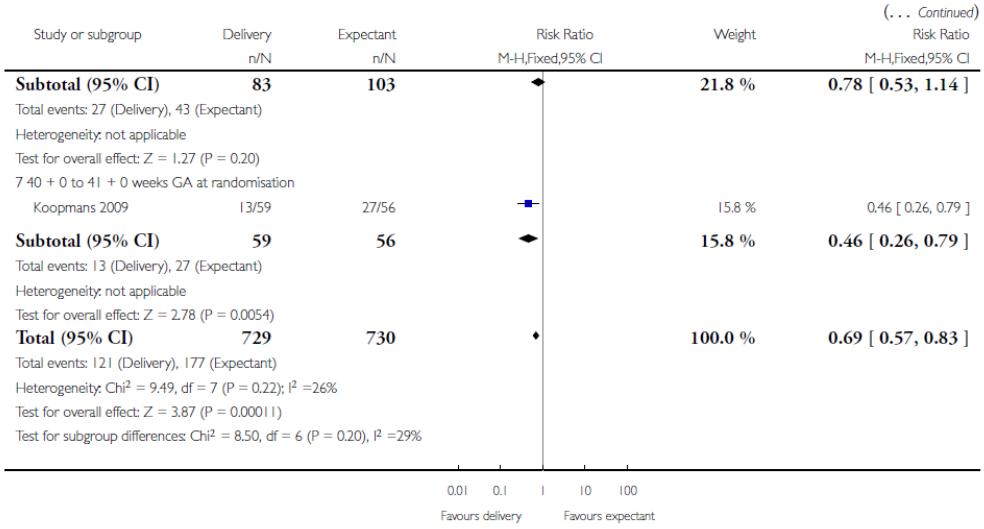
Comparison: 3 Planned early delivery versus expectant management (by each gestational week)

Outcome: 1 Composite maternal mortality and morbidity



(*Continued . . .*)

(. . . *Continued*)

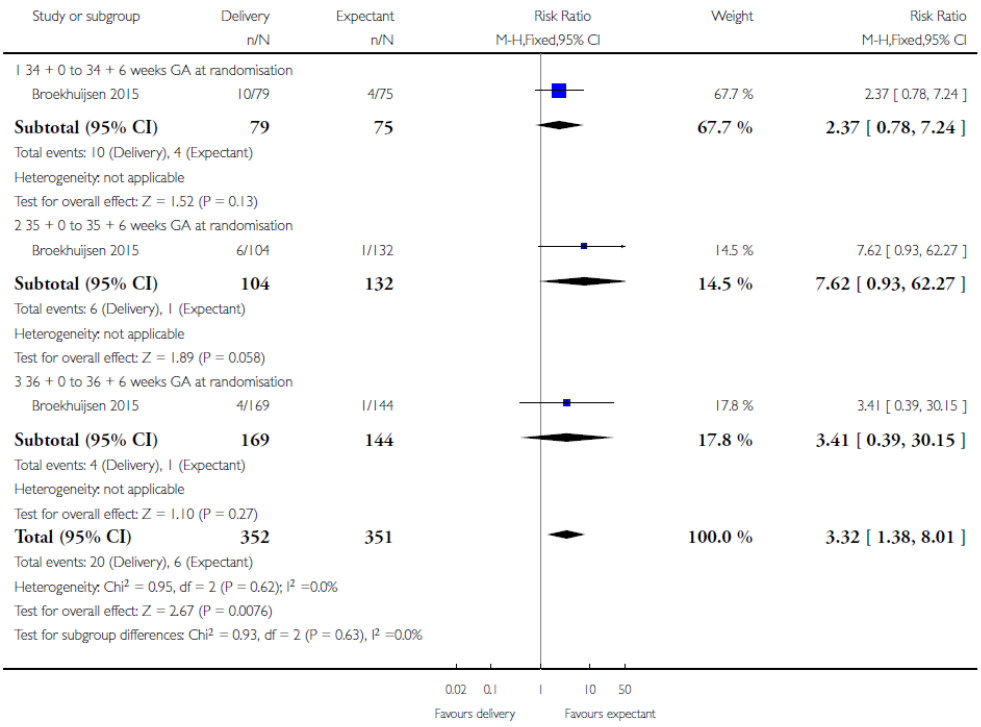


Analysis 3.2. Comparison 3 Planned early delivery versus expectant management (by each gestational week), Outcome 2 Respiratory distress syndrome.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 3 Planned early delivery versus expectant management (by each gestational week)

Outcome: 2 Respiratory distress syndrome

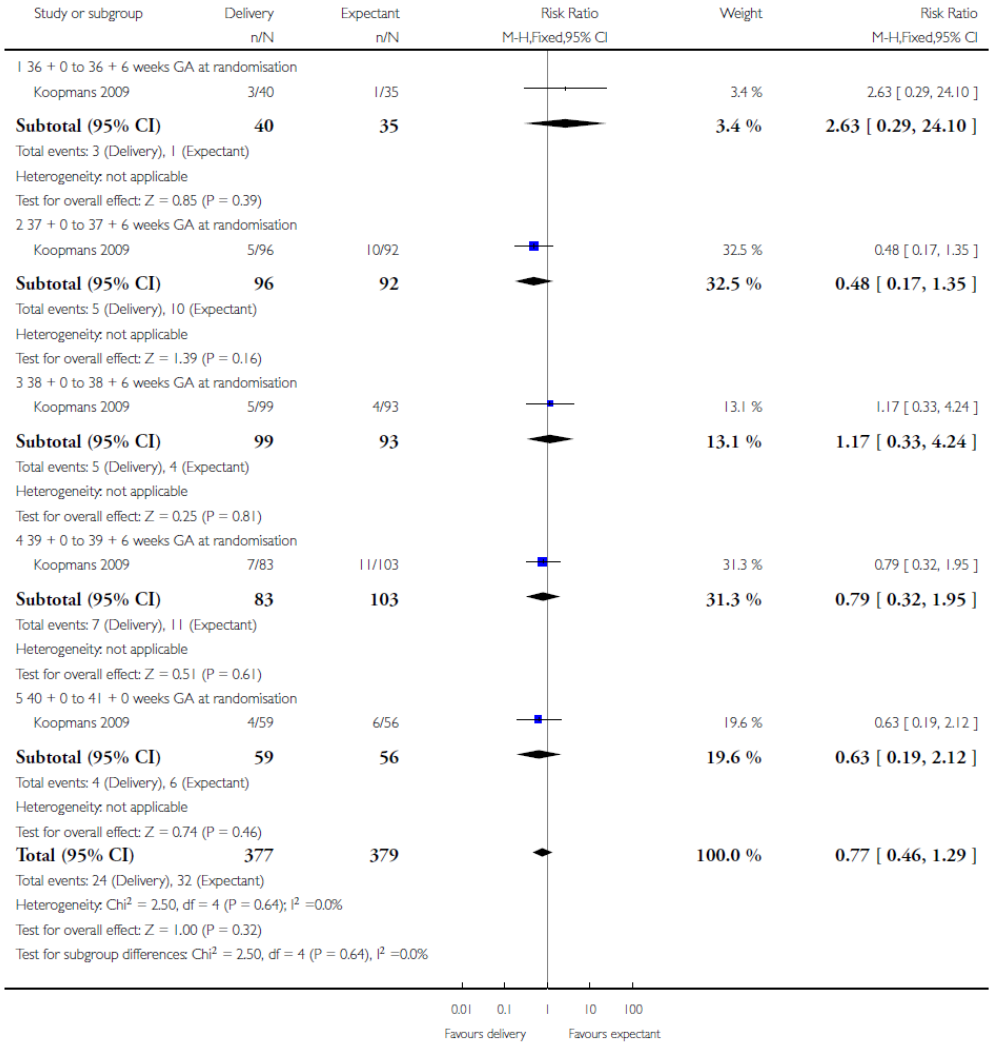


Analysis 3.3. Comparison 3 Planned early delivery versus expectant management (by each gestational week), Outcome 3 Composite infant mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 3 Planned early delivery versus expectant management (by each gestational week)

Outcome: 3 Composite infant mortality and morbidity



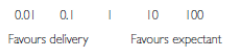
Analysis 4.1. Comparison 4 Planned early delivery versus expectant management (by condition), Outcome 1 Composite maternal mortality and morbidity.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 4 Planned early delivery versus expectant management (by condition)

Outcome: 1 Composite maternal mortality and morbidity

Study or subgroup	Delivery n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Gestational hypertension					
Broekhuijsen 2015	0/92	3/90		2.0 %	0.14 [0.01, 2.67]
Koopmans 2009	75/244	96/252		54.6 %	0.81 [0.63, 1.03]
Subtotal (95% CI)	**336**	**342**		**56.7 %**	**0.78 [0.61, 1.00]**
Total events: 75 (Delivery), 99 (Expectant)					
Heterogeneity: Chi^2 = 1.37, df = 1 (P = 0.24); I^2 =27%					
Test for overall effect: Z = 1.96 (P = 0.050)					
2 Mild pre-eclampsia					
Broekhuijsen 2015	2/165	4/159		2.4 %	0.48 [0.09, 2.59]
Koopmans 2009	41/123	67/123		38.7 %	0.61 [0.45, 0.82]
Subtotal (95% CI)	**288**	**282**		**41.1 %**	**0.60 [0.45, 0.81]**
Total events: 43 (Delivery), 71 (Expectant)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 3.34 (P = 0.00083)					
3 Chronic hypertension					
Broekhuijsen 2015	2/95	4/102		2.2 %	0.54 [0.10, 2.86]
Subtotal (95% CI)	**95**	**102**		**2.2 %**	**0.54 [0.10, 2.86]**
Total events: 2 (Delivery), 4 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
Total (95% CI)	**719**	**726**		**100.0 %**	**0.70 [0.58, 0.85]**
Total events: 120 (Delivery), 174 (Expectant)					
Heterogeneity: Chi^2 = 3.49, df = 4 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.68 (P = 0.00024)					
Test for subgroup differences: Chi^2 = 1.85, df = 2 (P = 0.40), I^2 =0.0%					

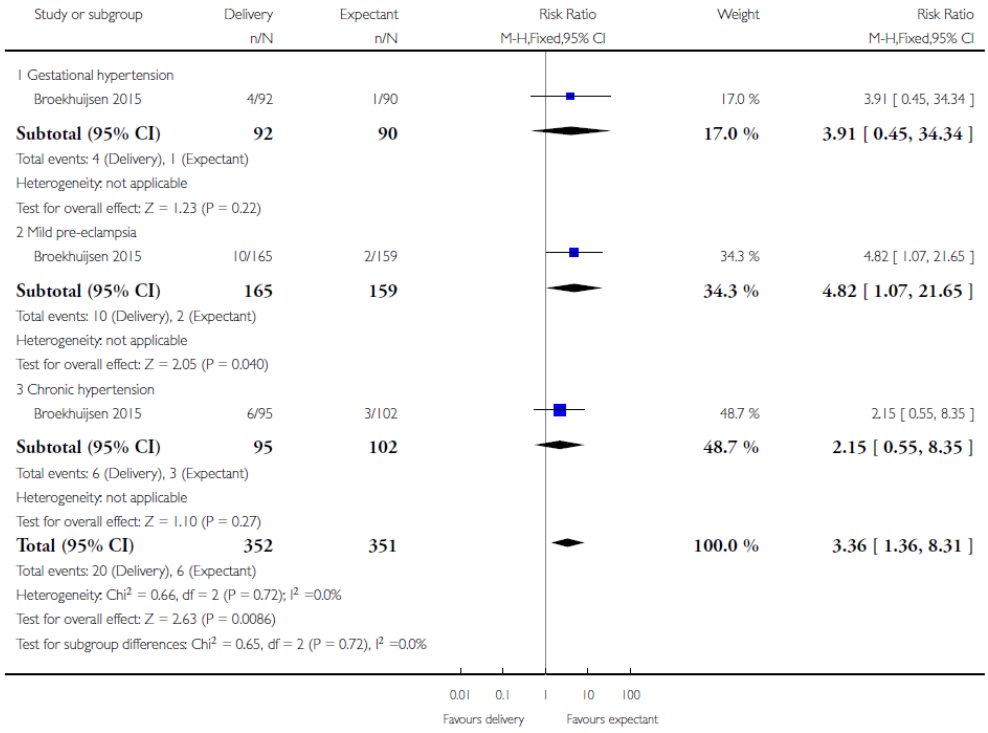


Analysis 4.2. Comparison 4 Planned early delivery versus expectant management (by condition), Outcome 2 Respiratory distress syndrome.

Review: Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term

Comparison: 4 Planned early delivery versus expectant management (by condition)

Outcome: 2 Respiratory distress syndrome



HISTORY

Date	Event	Description
14 January 2014	Amended	For clarification, the gestational age in the title has been changed from "at or near term" to "from 34 weeks to term"
12 December 2012	Amended	This scope of this protocol has been expanded to incorporate all hypertensive disorders of pregnancy and not just pre-eclampsia The methods section (Assessment of reporting biases/Subgroup analysis and investigation of heterogeneity) has been updated to incorporate the Cochrane Pregnancy and Childbirth Groups' updated standard methods text A new co-author (C M Koopmans) has joined the review team.

CONTRIBUTIONS OF AUTHORS

CC helped develop the protocol, extracted the data, checked data entry, helped write the review and is the guarantor for the review.

NN prepared the original protocol assisted and with the preparation of this review.

CK assisted with the preparation the protocol and review.

HW extracted the data, entered the data and helped write this review.

DECLARATIONS OF INTEREST

CK is an author of an included study in this review (Koopmans 2009). All decisions relating to this study (assessment for inclusion/exclusion, risk of bias and data extraction) were carried out by the other members of the review team who are not directly involved in the study.

HW is paid to work on Cochrane reviews by a grant to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

CC: none known.

NN: none known.

SOURCES OF SUPPORT

Internal sources

- (NN) Walter Sisulu Univeristy, East London Hospital Complex, South Africa.

NN was employed by East London Hospital Complex attached to Walter Sisulu University.

- (HW) Cochrane Pregnancy and Childbirth Group, Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK.
- (CC) Stellenbosch University, Cape Town, South Africa.

Cathy Cluver is registered for PhD at Stellenbosch University

External sources

- NIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines, UK.
- (CC) Discovery Foundation, South Africa.

CC has been awarded the Discovery Accademic Fellowship

- (CC) South African Medical Association, South Africa.

CC has been awarded the SAMA Fellowship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have edited the review title from *'Delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term'* to *'Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term'.*

Our Types of studies and Types of interventions sections have been edited to incorporate 'planned early delivery' as per the modified title.

The methods have been updated to reflect current standard methods text of Cochrane Pregnancy and Childbirth and we have updated some sections of the background.

We have used the GRADEpro Guideline Development Tool to assess the quality of the evidence included in this review. We have also include a Summary of findings for the main comparison.

Respiratory distress syndrome was analysed by subgroup, in addition to the prespecified composite maternal and infant outcomes, as the composite infant outcomes is not yet available by gestational age for Broekhuijsen 2015.

Changes to outcomes

Changes to maternal outcomes

We have made a number of changes to our protocol outcomes for maternal outcomes.

Primary outcome

The nature of the maternal composite outcome has been further clarified at the review stage:

- Protocol = Composite maternal outcome including maternal mortality (death during pregnancy or up to 42 days after end of pregnancy) and severe morbidity (eclampsia, stroke, renal or liver failure as defined below), haemolysis, elevated liver enzymes and low platelets syndrome (HELLP), disseminated intravascular coagulation (DIC), pulmonary oedema, thromboembolic disease, cardiac arrest, abruption of the placenta or antepartum haemorrhage).
- Review = ' Composite maternal outcome including maternal mortality (death during pregnancy or up to 42 days after delivery) and severe morbidity (eclampsia, cerebral vascular event, pulmonary oedema as defined by trial authors, severe renal impairment defined as a creatinine level greater than 125 μmol/l or a need for dialysis or urine output less than 0.5 mL/kg/hour for four hours unresponsive to hydration with two intravenous boluses, or as defined by trial authors, liver haematoma or rupture, liver failure defined as the rapid impairment of synthetic function and development of encephalopathy or as defined by trial authors, haemolysis

elevated liver enzymes and low platelets (HELLP) syndrome, disseminated intravascular coagulation (DIC), thromboembolic disease and abruptio placentae defined as a retroplacental clot of more than 15% of the maternal surface or as defined by trial authors.

Secondary outcomes

Our secondary outcomes edited accordingly:

- 'Death as defined above' has been edited to 'Maternal mortality as described above'
- 'Eclampsia (fitting)' has been edited to 'Eclampsia'
- Stroke (brain damage) has been edited to 'Cerebrovascular event'
- 'Pulmonary oedema (fluid in the lungs)' has been edited to 'Pulmonary oedema'
- 'Kidney failure (defined as rise in serum creatine concentration by > 1 mg/dL over baseline) and/or urine output less than 0.5 mL/kg/hr for two hours unresponsive to hydration with two intravenous boluses of 500 mL fluid), or as defined by trial authors' has been edited to 'Severe renal impairment as defined above'
- 'Liver failure (the rapid impairment of synthetic function and development of encephalopathy) or as defined by trial authors' has been edited to 'Liver failure as defined above'
- 'Abruption of the placenta or antepartum haemorrhage' has been split into two separate outcomes, 'Abruptio placentae' and 'Antepartum haemorrhage'
- 'Postpartum haemorrhage (blood loss 500 mL or more' has been edited to 'Postpartum haemorrhage (blood loss of more than 500 mL within 24 hours of delivery'

The following secondary outcomes have been added at the review stage:

- 'Liver haematoma or rupture'
- 'Admission to a high care or intensive care unit'

Changes to fetal/neonatal outcomes

We have made a number of changes to our protocol outcomes for fetal/neonatal outcomes:

Primary outcome

The nature of the perinatal composite outcome has been further clarified at the review stage:

- Protocol = Composite perinatal outcome (perinatal death (stillbirth or death in the first seven days of life), small-for-gestational age (growth below the third centile or lowest centile reported), acute respiratory distress syndrome (ARDS), necrotising enterocolitis (NEC), cerebral haemorrhage, Apgar score less than seven or very low (less than four) at five minutes, cord blood pH less than 7.1, neonatal seizures, intraventricular haemorrhage)
- Review = 'Composite perinatal outcome including fetal or neonatal death (within six weeks after the expected due date or as defined by trial authors), grade III or IV intraventricular or intracerebral haemorrhage, necrotising enterocolitis (NEC), acute respiratory distress syndrome (ARDS) or grade III/IV hyaline membrane disease, small-for-gestational age (growth below the 10th centile or as defined by trial authors) and neonatal seizures.

Secondary outcomes

Our secondary outcomes edited accordingly:

- 'Stillbirth', 'perinatal death' and 'neonatal death' have been replaced with 'fetal death', neonatal death (as defined in the primary outcome above).
- 'Intraventricular haemorrhage' has been edited to 'Grade III or IV intraventricular or intracerebral haemorrhage'.
- 'ARDS' has been edited to 'ARDS or grade III/IV hyaline membrane disease'
- The outcome 'small-for-gestational age' was changed to 'small-for-gestational age as defined by trial authors', with definitions given in the footnotes of the data
- 'Apgar score at five minutes: low (less than seven), very low (less than four) or lowest reported' has been replaced with 'Apgar score less than seven at five minutes'
- 'Cord blood pH less than 7.1' has been edited to 'Cord blood pH less than 7.1 or as defined by the trial authors'
- 'Endotracheal intubation or use of mechanical ventilation' has been edited to 'Intubation and mechanical ventilation or continuous positive airway pressure support'

The following secondary outcomes have been added at the review stage:

- 'Early neonatal sepsis'
- 'Surfactant use'
- 'Neonatal intensive care unit use or high care unit admission'

INDEX TERMS

Medical Subject Headings (MeSH)

*Cesarean Section [statistics & numerical data]; *Hypertension; *Labor, Induced [statistics & numerical data]; *Pregnancy Complications, Cardiovascular; *Watchful Waiting; Delivery, Obstetric; Gestational Age; Infant Mortality; Length of Stay; Maternal Mortality; Pre-Eclampsia; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy

6. References

1 Duley LM. The Global Impact of Pre-eclampsia and Eclampsia. In: Seminars in Perinatology. Elsevier, 2009: 130–7.

2 Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; **367**: 1066–74.

3 Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: A systematic review. Eur. J. Obstet. Gynecol. Reprod. Biol. 2013; **170**: 1–7.

4 Moodley J, Fawcus S, Pattinson R. Improvements in maternal mortality in South Africa. *South African Med J* 2018; **3**: s4–8.

5 Magee L, von Dadelszen P, Stones W, Mathai M, editors. The FIGO Textbook of Pregnancy Hypertension: An evidence-based guide to monitoring, prevention and management. London: The Global Library of Women's Medicine, 2016 http://www.glowm.com/pdf/NEW-Pregnancy_Hypertension-Final.pdf (accessed Oct 18, 2018).

6 Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens An Int J Women's Cardiovasc Heal* 2014; **4**: 105–45.

7 WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. Switzerland: WHO Library Cataloguing-in-Publication Data, 2011.

8 Moodley J. Saving Mothers 2011-2013: Sixth report on confidential enquiries into maternal deaths in South Africa, Short report. *Pretoria Dep Heal* 2014; : 1–365.

9 American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy.

Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122**: 1122–31.

10 Davey D, McGillivray I. The classification and defiinition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988; **158**: 892–8.

11 Brown MA, Magee LA, Kenny LC, *et al.* Hypertensive Disorders of Pregnancy. *Hypertension* 2018; **72**: 24–43.

12 Sibai BM. Preeclampsia As a Cause of Preterm and Late Preterm (Near-Term) Births. *Semin Perinatol* 2006; **30**: 16–9.

13 Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013; **209**: 544.e1-544.e12.

14 Cunningham FG, Lindheimer MD. Hypertension in Pregnancy. *N Engl J Med* 1992; **326**: 927–32.

15 Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular Trends in the Rates of Preeclampsia, Eclampsia, and Gestational Hypertension, United States, 1987-2004. *Am J Hypertens* 2008; **21**: 521–6.

16 Douglas KA, Redman CW. Eclampsia in the United Kingdom. *BMJ* 1994; **309**: 1395–400.

17 Knight M, UKOSS. Eclampsia in the United Kingdom 2005. *BJOG An Int J Obstet Gynaecol* 2007; **114**: 1072–8.

18 MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol* 2001; **97**: 533–8.

19 Simkhada B, Teijlingen ER van, Porter M, Simkhada P. Factors affecting the utilization of antenatal care in developing countries: systematic review of the literature. *J Adv Nurs* 2008; **61**: 244–60.

20 Banke-Thomas OE, Banke-Thomas AO, Ameh CA. Factors influencing utilisation of maternal health services by adolescent mothers in Low-and middle-income countries: a systematic review. *BMC Pregnancy Childbirth* 2017; **17**: 65.

21 Bhutta ZA, Black RE. Global maternal, newborn, and child health--so near and yet so far. *N Engl J Med* 2013; **369**: 2226–35.

22 Ghulmiyyah L, Sibai B. Maternal Mortality From Preeclampsia/Eclampsia. *Semin Perinatol* 2012; **36**: 56–9.

23 Say L, Chou D, Gemmill A, *et al.* Global Causes of Maternal Deaths: A WHO Systematic Analysis. *Lancet Glob Heal* 2014; **2**: 1–14.

24 Gruslin A, Lemyre B. Pre-eclampsia: fetal assessment and neonatal outcomes. *Best Pract Res Clin Obstet Gynaecol* 2011; **25**: 491–507.

25 Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2014; **348**: g2301–g2301.

26 Vogel JP, Souza JP, Mori R, *et al.* Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 2014; **121 Suppl 1**: 76–88.

27 Moore-Maxwell CA, Robboy SJ. Placental site trophoblastic tumor arising from antecedent molar pregnancy. *Gynecol Oncol* 2004; **92**: 708–12.

28 Nugent CE, Punch MR, Barr M, LeBlanc L, Johnson MP, Evans MI. Persistence of partial molar placenta and severe preeclampsia after selective termination in a twin pregnancy. *Obstet Gynecol* 1996; **87**: 829–31.

29 Matsuo K, Kooshesh S, Dinc M, Sun C-CJ, Kimura T, Baschat AA. Late postpartum eclampsia: report of two cases managed by uterine curettage and review of the literature. *Am J Perinatol* 2007; **24**: 257–66.

30 Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. *Am J Obstet Gynecol* 1996; **175**: 1365–70.

31 Phipps E, Prasanna D, Brima W, Jim B. Mini-Review Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines. *Clin J Am Soc Nephrol* 2016; **11**: 1102–13.

32 van der Merwe JL, Hall DR, Wright C, Schubert P, Grové D. Are early and late preeclampsia distinct subclasses of the disease--what does the placenta reveal? *Hypertens pregnancy* 2010; **29**: 457–67.

33 Raymond D, Peterson E. A Critical Review of Early-Onset and Late-Onset Preeclampsia. *Obstet Gynecol Surv* 2011; **66**: 497–506.

34 Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993; **341**: 1447–51.

35 Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. *JAMA J Am Med Assoc* 2002; **287**: 3183–6.

36 Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. *Annu Rev Pathol Mech Dis* 2010; **5**: 173–92.

37 Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a Disease of the Maternal Endothelium The Role of Antiangiogenic Factors and Implications for Later Cardiovascular Disease. *Circulation* 2011; **123**: 2856–69.

38 Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. In: Seminars in nephrology. Elsevier, 2011: 33–46.

39 Venkatesha S, Toporsian M, Lam C, *et al.* Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006; **12**: 642–9.

40 Maynard SE, Min JY, Merchan J, *et al.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003; **111**: 649–58.

41 Lawn JE, Blencowe H, Oza S, *et al.* Every Newborn: progress, priorities, and potential beyond survival. *Lancet* 2014; **384**: 189–205.

42 Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. Aggressive or expectant management for patients with severe preeclampsia between 28-34 weeks' gestation: a randomized controlled trial. *Obstet Gynecol* 1990; **76**: 1070.

43 Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: A randomized controlled trial. *Am J Obstet Gynecol* 1994; **171**: 818–22.

44 Publications Committee Society for Maternal-Fetal Medicine, Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. *Am J Obstet Gynecol* 2011; **205**: 191–8.

45 Hall DR. Understanding expectant management of pre-eclampsia. *Obstet Gynaecol Forum* 2016; **26**: 22–7.

46 Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset, severe pre-

eclampsia: maternal outcome. *BJOG An Int J Obstet Gynaecol* 2000; **107**: 1252–7.

47 Cluver C, Hannan N, van Papendorp E, *et al.* The Pre-eclampsia Intervention with Esomeprazole trial (PIE trial). *Am J Obstet Gynecol* 2018; **218**: S26–7.

48 Vigil-De Gracia P, Ludmir J. Perinatal and Hemodynamic Evaluation of Sildenafil Citrate for Preeclampsia Treatment. *Obstet Gynecol* 2016; **128**: 1181–2.

49 Magee LA, Yong PJ, Espinosa V, Côté AM, Chen I, von Dadelszen P. Expectant Management of Severe Preeclampsia Remote from Term: A Structured Systematic Review. *Hypertens Pregnancy* 2009; **28**: 312–47.

50 Chammas MF, Nguyen TM, Li MA, Nuwayhid BS, Castro LC. Expectant management of severe preterm preeclampsia: Is intrauterine growth restriction an indication for immediate delivery? *Am J Obstet Gynecol* 2000; **183**: 853–8.

51 McKinney D, Boyd H, Langager A, Oswald M, Pfister A, Warshak CR. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. *Am J Obstet Gynecol* 2016; **214**: 395.e1-395.e7.

52 Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). *Best Pract Res Clin Obstet Gynaecol* 2011; **25**: 463–76.

53 Broekhuijsen K, van Baaren G-J, van Pampus MG, *et al.* Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015; **385**: 2492–501.

54 von Dadelszen P, Magee LA, Benton SJ, *et al.* Activated protein C as disease-modifying therapy in antenatal preeclampsia: An open-label, single arm safety and efficacy trial. *Pregnancy Hypertens*

2018; **13**: 121–6.

55 Thadhani R, Kisner T, Hagmann H, *et al.* Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. *Circulation* 2011; **124**: 940–50.

56 Winkler K, Contini C, König B, *et al.* Treatment of very preterm preeclampsia via heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) apheresis: The Freiburg preeclampsia H.E.L.P.-Apheresis study. *Pregnancy Hypertens* 2018; **12**: 136–43.

57 Onda K, Hannan N, Beard S, *et al.* Proton pump inhibitors for treatment of preeclampsia. In: Pregnancy Hypertension. New Orleans, 2015: 3.

58 Onda K, Tong S, Beard S, *et al.* Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. *Hypertension* 2017; **69**: 457–68.

59 Shafik AN, Khattab MA, Osman AH. Magnesium sulfate versus esomeprazole impact on the neonates of preeclamptic rats. *Eur J Obstet Gynecol Reprod Biol* 2018; **225**: 236–42.

60 Saleh L, Samantar R, Garrelds IM, van den Meiracker AH, Visser W, Danser AHJ. Low Soluble Fms-Like Tyrosine Kinase-1, Endoglin, and Endothelin-1 Levels in Women With Confirmed or Suspected Preeclampsia Using Proton Pump Inhibitors. *Hypertens (Dallas, Tex 1979)* 2017; **70**: 594–600.

61 Cluver CA, Walker SP, Mol BW, *et al.* Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol. *BMJ Open* 2015; **5**: e008211.

62 Cluver CA, Hannan NJ, van Papendorp E, *et al.* Esomeprazole to treat women with preterm

preeclampsia: a randomised placebo controlled trial. *Am J Obstet Gynecol* 2018; published online July 25. DOI:10.1016/j.ajog.2018.07.019.

63 WHO. Strategies toward ending preventable maternal mortality (EPMM). 2015 http://apps.who.int/iris/bitstream/handle/10665/153544/9789241508483_eng.pdf;jsessionid=58BAE08CC833F9F33EAE4585FF0BFFE4?sequence=1 (accessed Nov 2, 2018).

64 Tan MY, Syngelaki A, Poon LC, *et al.* Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 186–95.

65 Poon LC, Wright D, Rolnik DL, *et al.* Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. *Am J Obstet Gynecol* 2017; **217**: 585.e1-585.e5.

66 Rolnik DL, Wright D, Poon LC, *et al.* Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med* 2017; **377**: 613–22.

7. Acknowledgements

I would like to thank the following people.

Professor Gerhard Theron, Professor Sue Walker and Professor Stephen Tong, my PhD promotors: Without your unwavering support, friendship, guidance, teaching and belief in me I would not have been able to complete this work. I will never be able to express my gratitude for everything you have done for me.

Sister Erika van Papendorp: You were with me every step of the way for the PIE trial. Thank you for your dedication to your work and our participants. You are sorely missed.

Dr Natalie Hannan, Sally Beard, Prof Ben Mol, Dr Richard Hiscock, Prof David Hall, Dr Eric DeCloedt, Kim Adams, Megan Rensburg, Pawel Schubert: Thank you to each of you for your role in the PIE trial.

Prof Hennie Botha: Thank you for your support over many years and for always believing in my potential.

Dr Natalia Novikova, Dr Corine Koopmans and Dr Helen West: Thank you for working with me on the Cochrane Review. It was a pleasure working with all of you.

Staff at Tygerberg Hospital in the Obstetrics Department: Thank you for your help in identifying potential participants, and for helping to collect samples. The PIE trial truly demonstrated how well we all work as a team.

I also thank all the participants of the PIE trial for volunteering to participate in our study.

And lastly, I thank my family, particularly my husband, who keeps me grounded, believes in me, and provides unconditional support, love and encouragement.

8. Funding

This project was made possible by generous contributions from the following organisations:

1. PhD scholarships from the Discovery Foundation, the South African Medical Association and Stellenbosch University
2. The Geoff and Helen Handbury Foundation, based in Australia.
3. The Norman Beischer Medical Foundation for Mothers and Babies, based in Melbourne.
4. The Mercy Foundation and Mercy Perinatal, based in Melbourne.
5. The Kilvington Trust, funding via the Department of Obstetrics and Gynaecology, University of Melbourne.