A prospective population-based study of preterm pre-labour rupture of membranes between 24 and 34 weeks of gestation in Cape Town Metro East- measuring protocol intervention fidelity and clinical outcome.

By N Mbungu

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Supervisor: GS Gebhardt

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

BACKGROUND: Preterm premature rupture of membranes (PPROM) complicates 2 to 3% of pregnancies and is associated with significant neonatal mortality and morbidity. Intrauterine infection is the most common cause of PPROM, approximately 50% overall.

OBJECTIVES: The primary objective of this study was to evaluate the quality of care delivered to women undergoing inpatient management with PPROM compared with a recently instituted hospital protocol. A secondary objective was to investigate the maternal and neonatal outcome of conservative management of PPROM 24-34 weeks in Tygerberg Hospital (TBH), and to determine the impact of the protocol on hospital stay (bed occupancy rate).

METHODS: A prospective population-based observational study on patients with confirmed PPROM managed conservatively, between 24 and 34 weeks gestation at TBH from 01 February 2014 to 31 January 2015. The charts of all patients (n=353) evaluated for possible PPROM were retrieved from the online TBH records system, Enterprise Content Management (ECM). Ninety-eight patients were eligible for the study.

RESULTS: The cumulative incidence of PPROM in the drainage region during this study period was 2.86 per 1000. The median gestational age was at delivery was 31 weeks and 4 days and most babies were appropriately grown for their gestation with but with 18 babies born below the 10th centile for birth weight according to their gestation. The median birth weight was 1690g. The most identifiable associated risk factor was cigarette smoking (35%). In 90% of patients with PPROM counselling was not done. Clear nursing prescriptions were not given in 90% of patients as per protocol and more than 65% of patients were not given betamethasone at correct intervals. Close to 60% of women were given antibiotics correctly and 86% of patients were checked for signs of chorioamnionitis twice day as per protocol. Most babies were admitted in high care with a median average stay of 8 days, but one stayed a maximum of 188

days and 6 babies died from severe prematurity. Other neonatal complications included neonatal jaundice (60%), respiratory distress (41%), sepsis (7%), necrotising enterocolitis (3%) and patent ductus arteriosus (4%). Total length of stay of mothers in hospital was a median of 6 days and none of the mothers had complications post-delivery.

CONCLUSION: PPROM is a serious complication of pregnancy and associated with low birth weight, preterm delivery significant perinatal morbidity and mortality and prolonged hospital stay, however it does not have major impact on maternal outcome as seen in this study. More attention needs to be given to provide adequate counselling for women admitted with PPROM and train nursing personnel to administer BMZ and antibiotics as prescribed.

Opsomming

AGTERGROND: Voortydse voorkraamse ruptuur van vliese (VVRVV) kompliseer 2-3% van alle swangerskappe en veroorsaak betekenisvolle morbiditeit en mortaliteit. Die mees algemene oorsaak, in amper 50% van gevalle, is intra-uteriene infeksie.

DOEL: Die hoofdoel van hierdie studie was om die kwaliteit van sorg te evalueer wat aangebied is aan vrouens wat toegelaat is met VVRVV. Die standaard waarteen die sorg gemeet was, was 'n protokol vir die hantering van VVRVV wat kort vantevore implementeer is. 'n Bykomende doel was om na die uitkoms van moeders en babas te kyk wat konserwatiewe hantering vir VVRVV ondergaan het. Daarby was gekyk na die impak wat die protokol op bedbesetting het.

METODE: Hierdie was 'n prospektiewe bevolkings-gebaseerde waarnemingsstudie op pasiënte met bevestigde VVRVV tussen 24 en 34 weke wat toegelaat is vir konserwatiewe hantering by Tygerberg Hospitaal (TBH). Die tydperk van evaluasie was 01 Februarie 2014 tot 31 Januarie 2015. Die notas van alle pasiënte met vermoedelike VVRVV was deurgegaan op die aanlyn sisteem *Enterprise Content Management*. Agt-en-negentig vrouens het aan die toelatingsvereistes vir die studie voldoen.

RESULTATE: Die insidensie van VVRVV in die hele gesondheidsdistrik was 2.86 per 1000 tydens die studie periode. Die mediane swangerskapsduur met verlossing was 31 weke en 4 dae. Meeste babas was toepaslik gegroei vir hulle swangerskapsduur, maar 18 was kleiner as verwag (klein vir datums, gedefinieër as 'n geboortegewig onder die 10de persentiel). Die mediane geboortegewig was 1690g. Die mees algemene faktor wat verband gehou het met VVRVV was sigaretrook, in 35% van gevalle. Negentig present van alle vrouens het geen raadgewing met toelating ontvang nie. Dieselfde persentasie is toegelaat sonder duidelike verpleegvoorskrifte en 65% van vrouens het nie die voorgeskryfde steroïed behandeling op

die regte tyd gekry nie. Amper 60% van vrouens het antibiotika op die regte tyd ontvang en 86% is daagliks ondersoek vir tekens van infeksie. Meeste babas het hoë sorg behandeling verkry en die mediane verblyf in die eenheid was 8 dae. Een baba het 188 dae behandeling benodig en 6 is oorlede aan erge prematuriteit. Ander komplikasies vir die babas was geelsug (60%), asemhalingsnood (41%), infeksie (7%) en nekrotiserende enterokolitis (3%). Die mediane verblyf van die moeders was 6 dae en geen van hulle het enige ernstige kompliksies gehad nie.

GEVOLGTREKKING: VVRVV is 'n ernstige komplikasie van swangerskap en hou verband met lae geboortegewig, voortydse kraam en betekenisvolle morbiditiet en mortaliteit vir die babas. Dis belangrik dat alle vrouens met die probleem goeie raadgewing ontvang met toelating sodat hulle bewus is van die omvang van die probleem.

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List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AF	Amniotic fluid
AFI	Amniotic fluid index
ALT	Alanine amino transferase
AP	Abruptio placenta
AST	Aspartate amino transferase
BMI	Body mass index
BMZ	Betamethasone
CA	Chorioamnion
CAM	Chorioamnionitis
CL	Cervical length
CRP	C-reactive protein
CS	Caesarean section
CTG	Cardiotocography
EC	Escherichia coli
ECM	Enterprise Content Management
EM	Expectant management
fFN	Fetal fibronectin
GA	Gestational age
GBS	Group B streptococcus
HIV	Human immune deficiency virus
HMD	Hyaline membrane disease
ID	Immediate delivery
IGFBP-1	Insulin-like growth factor binding protein-1
IOL	Induction of labour
IVH	Intraventricular haemorrhage
MMPs	Metalloproteinases

MOU	Midwife obstetric unit
NEC	Necrotising enterocolitis
NJ	Neonatal jaundice
PDA	Patent ductus arteriosus
PAMG -1	Placental alpha macroglobulin -1
PTB	Preterm birth
PMN	Polymorphonuclear
pPPROM	Previable preterm premature rupture of membranes
PPROM	Preterm premature rupture of membranes
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory distress syndrome
ROM	Rupture of membranes
SROM	Spontaneous rupture of membranes
TBH	Tygerberg Hospital
TVS/U	Transvaginal scan/ ultrasound
WBC	White blood cell

1. Background

1.1 Introduction

Preterm Premature Rupture of Membranes (PPROM) is an important problem in Obstetrics. The consequences can be very serious, as the risk of neonatal morbidity and mortality is very high and there is an increased risk of maternal morbidity from infection or sepsis. It is very crucial to fully inform patients about the severity of PPROM complications, as the management of these morbidities related to PPROM constitute a significant challenge (1).   Infection is the main cause of, or result from, PPROM (2).

1.2 Amniotic fluid and fetal membranes

The fetal membranes (chorioamnion) are made up of two membranes, the outer chorion and inner amnion that enclose the amnion cavity which contains amniotic fluid (AF) (3), both derived from the fetal tissue (4).   They are formed during second and third trimester of pregnancy. The amnion consists of a single layer of cuboidal cells and collagen. The chorion is thicker than the amnion and consists of reticular and trophoblastic cells and is directly attached to the maternal decidua (4) . The strength of the fetal membrane comes from the collagen in amnion and the attachment of these two membranes to each other (5). They have a highly protective function against infection and trauma for the growing fetus in utero and also promote an environment where amniotic fluid can accumulate, which is important for survival of the fetus in utero (5) as it is responsible for fetal development and growth (6). In addition, amniotic fluid also protects against infection as it has some bacteriostatic properties, and decreased amniotic fluid causes an increased risk of infection (7).   Therefore, it is very important for the membranes to remain intact until the onset of labour at term to maintain this protective intrauterine fluid environment.

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1.3 Definitions

Premature rupture of membranes (PROM) is spontaneous rupture of the amniotic membrane with a release of amniotic fluid at least one hour before the labour begins, whereas **PPROM** is prelabour (prior to the onset of labour) rupture of membranes before 37 completed weeks (8)(9)(10). PPROM is divided into three groups **: pre-viable PPROM** (< 23 weeks), **PPROM remote from term** (from 24 to 32 weeks of gestation), and **PPROM near term** (32 to 36 weeks of gestation) (11).

Latent period – it is defined as the period between rupture of the membranes and the onset of labour (12). Few pregnancies can reach term following PPROM. Approximately 50% deliver within one week, 70-75% within 2 weeks and 80- 85% by 28 days following rupture; but the degree of latency varies according to the gestational age at the time of rupture of membranes, with the labour onset being inversely correlated with gestational age (13).

1.4 Incidence

PPROM complicates 2 to 3% of pregnancies but is associated with 40% of preterm deliveries globally, which result in significant neonatal mortality and morbidity (14)(15)(16). According to most studies, the incidence of PPROM varies for different countries and population. This could be could be due to the multiple risk factors that are associated with PPROM. According to a retrospective study done in Nigeria by Okeke and colleagues over a period of 10 years (1998-2008), the incidence of PPROM was 3.3% (17). In Southern Africa the incidence varies significantly in different populations and figures between 5-40% have been reported (18).

1.5 Risk factors for PPROM

Normally, the membranes rupture during labour. There are many risk factors associated with PPROM but none of them is known to be directly etiologic. The exact reason for ruopture of membranes (ROM) before labour therefor remains unknown. Risk factors include infections, cervical incompetence, uterine over-distension as in multiple gestation or polyhydramnios, low socio economic status, previous history of PPROM and smoking or vaginal bleeding. (12)(19).

1.5.1 Infection

Intrauterine infection is the most common cause of PPROM, approximately 50% overall (20) and thought to be the main risk factor for adverse neonatal outcome, such as cerebral palsy (21). About one-third of pregnancies complicated by PPROM will have a positive amniotic fluid (AF) culture and it has been shown in studies that bacteria have the potential to cross the intact chorioamniotic membrane (15)(22). Most bacteria that are associated with PPROM originate from the vagina and cross through the chorioamniotic membranes; then enter the amniotic fluid via direct ascension (20) .

Clinical chorioamnionitis is present in 1-2 % of women with PPROM presenting the first time, and subsequently develops in 3-8% of women (22). Most cases with infection in the AF is asymptomatic and do not meet the diagnostic criteria for clinical chorioamnionitis. There are certain bacteria that have been demonstrated in microbiologic studies to predispose women to PPROM via several mechanisms: Bacteroides species, *Trichomonas vaginalis*, *Neisseria gonorrhoea*, Group B streptococcus and *Chlamydia trachomatis* have been associated with an increased incidence of PPROM (12).

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Other micro-organisms demonstrated in positive vaginal cultures in women with PPROM were *Escherichia coli, Gardnerella vaginalis, Proteus vaginalis,* staphylococcus species and *Pseudomonas aeruginosa* (23) as well as *Ureoplasma urealyticum* (24).

1.5.2 Previous PPROM or preterm delivery

Previous PPROM or preterm delivery cause an increase incidence of PPROM in the current pregnancy. Van de Hayden and associates showed an increased recurrence risk of 9% in women with PPROM before 27 weeks and for subsequent pregnancy the risk is about 35% (25).

1.5.3 Smoking

The association between smoking and PPROM is controversial, but Andres et al showed no difference in the incidence of PPROM when comparing non-smokers to smokers (19).

1.5.4 Iatrogenic causes

Diagnostic procedures such as amniocentesis and chorionic villus sampling increase the risk of PPROM. The risk for amniotic fluid leakage following invasive testing is approximately 1-3% (5). Procedures such as emergency cervical cerclage in the presence of bulging membranes can cause PPROM.

1.5.5 Uterine distension

The risk of PPROM is increased in polyhydramnios or multiple pregnancy, as these both cause increase pressure on the membrane, stretching it causing weakening of the membranes.

1.5.6 Cervical incompetence and shortening

Cervical length (CL) below 25 mm on transvaginal scan (TVS) (13)(26) is associated with high risk of infection such as chorioamnionitis (27). But, the controversy over the use of TVS to predict preterm birth (PTB) and diagnosis of spontaneous preterm labour persists. One study showed that high risk women based on past obstetric history with a CL shorter than 25 mm on TVS detected in the early second trimester are at high risk for PTB, whereas those with CL below 10 mm with cervical funnelling have increased risk of PPROM (13). A closed internal cervical os is unlikely to allow ascending infection as compared to the one that is open. Lee and co-workers showed that a short CL (less than 15mm) in PPROM is associated with high risk for amniotic inflammation/infection and imminent preterm delivery, independent of the existing intra-amniotic inflammation or infection (28).

1.5.7 Dietary habits

Micronutrients deficiencies such as Vitamin C or ascorbic acid have been shown to alter collagen structure and this increases the risk of PPROM (29). Others include zinc and vitamin E.

1.5.8 Other risk factors:

Poor socio economic status, no antenatal care, coitus in the second half of pregnancy if at risk of sexually transmitted disease, abuse of alcohol (18) and occupational factors such as strenuous physical work (13) are all associated with PPROM.

1.6 Mechanism or pathogenesis of PPROM

PPROM occurs suddenly and unpredictably. The pathogenesis of PPROM is thought to be due to a combination of biochemical weakening of the chorio-amnion (CA) and physical stresses. Inflammation of the CA within the AF plays a major role in the pathogenesis of PPROM (3). In normal pregnancy weakening of the membranes occurs close to term (37- 41 weeks gestation) prior to the onset of labour. The chorion is thicker but very weak as compared to the amnion suggesting that biochemical failure of structural components unique to amnion may be critical for membrane rupture (3).

Microorganisms produce mucinases and proteases which allow them to break down secretory immunoglobulin A and to penetrate the cervical mucosa plug. Thereafter, they release collagenases and elastases (13) that directly damage or weaken the collagen in the membrane (12) and a decrease in the collagen content of the membrane increases the risk of PPROM (9).

The other theory for the pathogenesis of PPROM is that bacterial invasion of the choriodecidual space stimulates the amniotic membrane and decidua to release a number of proinflammatory

cytokines including granulocyte colony factor, tumour necrosis factor A and interleukins (-1a; -1b;-6;-8) (20).   These pro-inflammatory cytokines activate the synthesis of bioactive substances like prostaglandins and matrix metalloproteinases (9). The prostaglandins initiate cervical changes and uterine contractions, which further weaken the membrane.   The metalloproteinases (MMPs) are zinc dependent enzymes capable of degrading extracellular matrix macromolecules or their components such as glycoproteins, proteoglycans and collagen. These enzymes have been implicated in remodelling as part of both pathological and physiological and process (13). Membrane rupture, which is an integral part of human parturition, may be either pathological or physiological. Therefore, these enzymes degrade connective tissue such as chorioamnion membranes leading to rupture (20) and relax and soften the cervix by remodelling the collagen which further leading to membrane rupture (13).
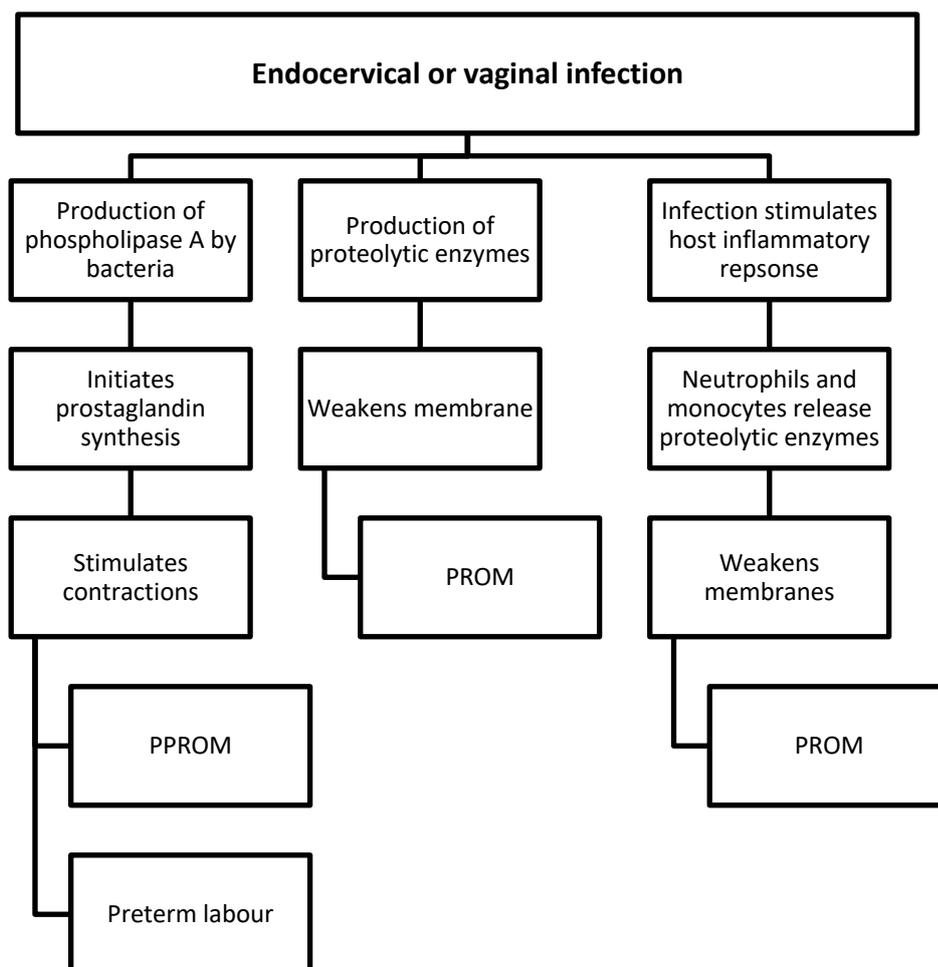
Figure 1: Mechanisms of how infection causes PPROM

(Adapted from Kavak et al (11)).

Jeroen and associates showed that weakening of CA membrane also occurs through mechanism of down regulation of amniocyte cytokeratin synthesis, which are components of intermediate filaments important for maintaining elasticity, cellular structure, resisting shear and this causes the amnion to be vulnerable to shear stress , apoptosis and rupture (3).

1.7 Diagnosis of PPROM

The diagnosis of PPROM is very important to avoid serious maternal and fetal complications associated with it. The diagnosis of PPROM is made on history, physical examination and simple side room or laboratory tests. On history, patients may give a history of a sudden gush of fluid running down the legs from the vagina followed by uncontrollable leaking. In 90% of the time, history of PPROM given by the patient is always correct. The standard tests are based on determination of pH or a ferning pattern of salts in amniotic fluid as seen under microscopy. These tests are not 100% accurate, they have false positive and false negative results. This is due to factors such as scanty residual amniotic fluid in the vaginal vault, maternal urinary incontinence and the presence of semen or blood.

1.7.1 Sterile speculum

Digital examination should be avoided as it increases the risk of infection (22) and prostaglandin release with the risk of preterm labour, unless there is evidence that the woman might be in active labour (15). The diagnosis of PPROM is easily made when amniotic fluid is visualised in the vagina or fluid coming from the cervix on speculum examination. If the fluid is present, slight fundal pressure may be applied to facilitate visualisation and collection of fluid, and sometimes it is useful to ask the patient to cough or strain down. The fluid is best collected from the posterior vaginal fornix at the base of the cervix for laboratory tests (12).

1.7.2 Litmus test

It is the most widely used test, and it detects PH changes (15). The litmus test is based upon the changes in colour of the litmus paper when exposed to fluids with differing pH values. The vaginal pH normally ranges between 4.5 and 6.0 (pink on litmus paper), whereas the amniotic fluid has a pH of 6.5 or more (dark blue) (12). The accuracy of the test is approximately 74% to 95% (12). The presence of bacterial vaginosis, urine, semen, soap, cervicitis, alkaline , blood and antiseptic solution may give false positive results (22). To increase accuracy of the test, a sample of fluid can be collected from the vaginal pool in the posterior fornix with a sterile cotton swab and test the swab with litmus paper (12).

1.7.3 Ferning test

The fern test is accurate 70% to 98% of the time (12). When the amniotic fluid is dried on a clean slide and visualised under low (10x) power through a microscope, a characteristic arborisation or fern pattern is seen and that is diagnostic for the presence of amniotic fluid. The accuracy of the fern test improves markedly with time. Studies have demonstrated that on a slide known to have amniotic fluid (from amniocentesis sample), 86% are fern positive at 3 minutes and 100% are fern positive at 10 minutes (12). Therefore, the false negative rate increases with less time or with flame drying (22). False negatives are also possible if the patient has had a high (intermittent) leak and is being examined more than two hours after the initial episode (12). If results are inconclusive, including the litmus test, the patient needs to be placed in a semi Fowler's position and repeat the speculum examination in 30 minutes.

1.7.4 Ultrasound

Ultrasound assessment of the amount of amniotic fluid around the fetus may be useful as adjunctive data, but because oligohydramnios can exist as a separate entity, a low amniotic fluid volume seen on an ultrasound is not diagnostic for PPROM (12). Theoretically reduced or absent (AFI) in a patient with a suspicious history of PPROM could be used as evidence of ROM.

1.7.5 Other tests

The diagnosis of PPROM is very difficult after 48 hours or more. In most cases, positive or negative results of fern or litmus tests are meaningless (26) .

1.7.5.1 Aspartate Amino Transferase (AST)

Liver enzymes such as AST and Alanine Amino Transferase (ALT) are produced by fetus and secreted in amniotic fluid and there is no relation between their amount and that of maternal enzymes (26). According to Asgharnia et al, measurement of the AST level in vaginal fluid can be used as a reliable test for diagnosis of PPROM. In their study, they showed a significant difference between the AST levels of PPROM and that of the normal group, with the sensitivity, specificity and positive and negative predictive value of 91, 83, 80 and 93% respectively (26).

1.7.5.2 Amnisure ROM and Actim PROM test

These are the non-invasive tests that use a simple dipstick test format to detect specific proteins in the amniotic fluid (30) . The Actim PROM™ (Medix Biochemica) detects insulin-like growth factor binding protein -1 (IGFBP-1), and Amnisure™ (Qiagen) detects the presence of placental alpha macroglobulin-1 (PAMG-1) (31). The IGFBP-1 is synthesised in the fetal liver and decidual cells and found in the amniotic fluid throughout pregnancy (30) . A sterile polyester swab is used to collect samples for both tests before TVU or vaginal examination from vaginal fluid, and then the swab is placed in a buffer containing a solvent, with the lower end of the strip submerged (30). The Amnisure™ has been shown to be more accurate in the diagnosis of membrane rupture with a specificity and sensitivity of 100% and 98.9% respectively (15) (32). According to Ramsauer et al, the PAMG-1 test is more specific and sensitive compared to IGFBP-1 (31).

1.7.5.3 Fetal fibronectin (fFN)

Fetal fibronectin is a member of extracellular matrix family and a complex adhesive glycoprotein that is found at the maternal fetal interface. It is expressed in the extracellular matrix found in the choriodecidual junction between the fetal membranes and maternal decidual as well as in the placenta and uterus during pregnancy. It is found towards end of second trimester in pregnancy, where it may reflect normal growth of the placenta and trophoblasts. It is absent between 22 and 34 weeks gestation, and then is detectable again after 34 weeks until term. It is thought to be a trophoblast glue that promotes cellular adhesion at uterine-placental and decidual fetal membrane interface. It is released into cervicovaginal secretions when the extracellular matrix of the chorionic/decidual interface is disrupted (33), due to mechanical factors such as uterine contraction or rupture of membranes (34).

According to Goffeng et al, vaginal fFN is a good marker for fetal membrane rupture (34). fFN is more sensitive and specific than ferning and litmus tests with a sensitivity and specificity of 94.5 and 89.1 of fFN respectively as compared with 84.5% sensitivity and 78.2% specificity for ferning test and 87.3% sensitivity and 80.9 % specificity for litmus test (33). De Carolis and associates showed high fFN levels in the cervicovaginal secretions during the period of membrane rupture and subsequently a drop of fFN levels during the period of spontaneous resolution of membrane rupture (35).

1.7.5.4 The intra-amniotic injection of indigo carmine dye

This is impractical for routine use and its use remains very limited (31).

1.8 Maternal and fetal complications associated with PPROM

1.8.1 Maternal complications

1.8.1.1 Infection

The risk of chorioamnionitis is 10 times more for each day a preterm fetus stays in the uterus with PPROM (9). The incidence of chorioamnionitis (CAM) when PPROM occurs ranges between 5%-10% for those women with latent periods greater 24 hours, compared with a general incidence of 1%-2% in women with latent periods less than 24 hours (12). Most studies have shown the incidence of CAM to be approximately four times higher in patients with PPROM compared to patients without PPROM (9). The highest incidence of chorioamnionitis is associated with prolonged latent period and decreasing gestational age (36). In contrast, Stewart et al showed no difference in the incidence of chorioamnionitis related to the latent

period (37) . CAM is associated with a high possibility of failed induction of labour resulting in caesarean section in patients with PPROM (9)(38).

The diagnosis of chorioamnionitis is clinical and is diagnosed before delivery. It is considered to be a risk factor for increasing rates of neonatal sepsis, premature birth with respiratory distress syndrome, perinatal death, cerebral palsy and post-partum maternal infection (39)(10)(40)(41). The diagnosis for clinical CAM requires the presence of fetal tachycardia, maternal fever (37.5º C or more), uterine tenderness, maternal tachycardia, foul smelling amniotic fluid or maternal leucocytosis (white blood cell (WBC) count of more 15 000/ml^3)(39).

There is controversy in the literature regarding the accuracy of the laboratory tests of raised C- reactive protein (CRP) and leucocytosis in the prediction of clinical chorioamnionitis with ranges from 5% to 47% (14). CRP is known as an inflammatory biomarker that is released in response to infection, acute injury or other inflammatory stimuli, but does not specify the location or the condition causing inflammation (42). Smith et al failed to show a strong correlation between CRP and clinical or histologic CAM, therefore the routine use of CRP level as an isolated prediction in the management of patient with PPROM is not recommended (39).

There is not enough evidence to recommend the use of the amniocentesis in diagnosing intrauterine infection, however, it is probably beneficial in the 30 to 34 week gestation group when knowledge of lung maturity is an important consideration that could influence management significantly (12). Amniocentesis has the ability to detect subclinical infection in asymptomatic patients- approximately 25% to 30% (positive amniotic fluid culture) in patients with PPROM (7)(14) before the onset of clinical chorioamnionitis and fetal sepsis. This may allow appropriate and timeous management such as administration of antibiotics, expectant management for patients with negative AF cultures and/or delivery depending on the gestation (15). In addition to culturing the amniotic fluid to identify microbial colonisation, the fluid can

also be evaluated for glucose and cytokines such as interleukin 6 and 18, which can indicate intrauterine infection (15)(39)(43).

Histologic CAM refers to CAM that is confirmed after delivery by means of histologic evaluation, which detects pathogens in usually sterile tissues (39). It occurs in 60% of patient with PPROM (6).

1.8.1.2 Abruptio placenta (AP)

The incidence of AP in PPROM ranges between 4%-12%, usually a concealed abruptio (9)(36). The cause of placental abruptio in PPROM remains largely speculative. Ananth et al showed intrauterine infection as a strong risk factor for placental abruption (44). Secondly, oligohydramnios in the presence of PPROM increases the risk of placental abruption and thirdly, women with PPROM managed expectantly are at increased risk of developing abruptio placenta if the latent period exceeds 24 hours (44). One of the theories regarding pathophysiology of abruptio placenta in PPROM is that acute reduction in the uterine volume and intrauterine surface area as a consequence of (preterm) PROM can subsequently lead to a disruption of the placental site attached to the decidual spongiosa layer, thereby predisposing to AP (44).

1.8.2 Fetal Complications

PPROM leads to one third of all causes of preterm birth and causes 40-75% neonatal death. The fetal and neonatal mortality and morbidity risks are significantly affected by severity of oligohydramnios, and gestation at PPROM and duration of latency (45). Lorthe et al found that prolonged latency after PPROM does not aggravate neonatal prognosis for a specified gestational age at birth (46). Souza et al showed that severe oligohydramnios (AFI <5cm) is

associated with high perinatal complications and death (47). Morbidity and mortality in premature infants becomes higher with decreasing gestational age and birth weight. The causes of mortality associated with PPROM are discussed below:

1.8.2.1 Pulmonary hypoplasia

Pulmonary hypoplasia occurs most common at PROM less than 29 weeks gestation. It is associated with gestational age at the time of rupture of the membranes, oligohydramnios during latency and the duration of latency. PPROM that occurs in early gestation is associated with increased risk of pulmonary hypoplasia (36). Following a period of prolonged oligohydramnios, a proportion of infants develop pulmonary hypoplasia. Their lung to body weight ratio and total lung DNA are reduced and the radial alveolar count is decreased and the pulmonary vascular bed is reduced in size with a decreased vessel count and increased pulmonary vascular muscular development (43). Persistent oligohydramnios leads to poor alveolar development and this becomes evident with failure of lung growth despite prolonged latency (45).

Although loss of lung fluid, fetal compression and lack of breathing movements have all been implicated in pulmonary hypoplasia, loss of lung fluid appears to remove the fluid amount important for continuing lung development (36). Reduced amniotic fluid volume is associated with increased chest compression, reducing fetal breathing movements and causing an outflow ('squeeze') of lung fluid from fetus (43).

Even though the use of antenatal steroids and use of exogenous surfactant has markedly reduced the mortality and morbidity associated with respiratory distress syndrome (RDS), infants suffering from RDS remain at high risk of having increased susceptibility of diseases such as respiratory syncytial virus infection and chronic lung diseases (36).

1.8.2.2 Intraventricular haemorrhage (IVH)

It causes a significant morbidity in premature infants and is seen in 20% of infants born less than 32 weeks gestation. Intraventricular haemorrhage along with central nervous system parenchymal echo densities and periventricular leukomalacia increase with decreasing GA especially if pregnancy or neonate is associated with other complications. These abnormalities are associated with abnormal neurodevelopmental outcome including cerebral palsy. The risk of developing cerebral palsy is always increased in prolonged PPROM and CAM (36)(45)(14)(16). A significant association between IVH with clinical CAM or placental inflammation has been reported in preterm birth (10).

1.8.2.3 Fetal restriction deformities

In addition to pulmonary hypoplasia, reduced liquor at early gestational age is associated with restrictive deformations secondary prolonged compression and lack of fetal movements (45). The deformities include spade like hands and flexion contractions of the elbows, knees and feet. This is called the oligohydramnios sequence suggesting that the primary cause is the oligohydramnios (36) and the deformities are similar those seen in Potter's syndrome (45).

1.8.2.4 Cord prolapse

It occurs in 1% to 2% of cases with PPROM but has been reported to occur often in multiple gestation- approximately 6% of cases (36).

1.8.2.5 Cord compression

It results from both lack of a cushioning effect of the amniotic fluid and prolapsed cord (36).

1.8.3 Complications from labour and delivery

The most common complication is fetal distress and it is usually secondary to other complications such as cord compression/prolapse, abruptio placenta and infection. This requires emergency caesarean section resulting in low 5-minute Apgar scores in 2% to 20% of cases (36).

1.8.3.1 Sepsis

The incidence of sepsis is approximately 1% in the neonates born to mothers with ROM more than 24 hours. When clinical CAM is present the risk of proven sepsis increases to 3% - 5%. When prolonged ROM is accompanied with prematurity, the incidence of proven sepsis is 4-6% (45).The risk of neonatal sepsis increases with decreasing gestational age and when associated with maternal CAM it has been reported as high as 36% at less than 26 weeks gestation. *Escherichia coli* and Group B Streptococcus are the most common bacterial causes of sepsis associated with PPROM and CAM (36).

1.8.4 Other complications

Other associated complications include necrotising enterocolitis (NEC), Patent Ductus Arteriosus (PDA) and prolonged stay in the neonatal intensive care unit post-delivery (48).

1.9 Management of PPROM

1.9.1 Use of tocolytic drugs

The use of tocolytic drugs after PPROM remains controversial as PPROM is frequently associated with subclinical CAM (11). Tocolysis has not been found to be effective and tocolytic drugs have not proved their effectiveness whether in terms of improving perinatal outcome, as a prophylactic treatment for onset of labour, or as curative treatment after onset of uterine contractions. Currently accepted indications are to allow antenatal corticosteroids to take effect or for in utero transfer (49)(50).

1.9.2 Use of corticosteroids

Antenatal corticosteroids have been shown to decrease the risks of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and as well neonatal death in preterm neonates (51)(15)(8). However, Glasner et al showed that steroids impair the maternal polymorphonuclear leukocyte (PMN) - based immune system, which is the first line of defence mechanism against fungal and bacterial pathogens and in order for host defence to be effective, the PMN- based immune system must remain intact. This explains why there is still serious prenatal and postnatal bacterial infections of child and mother in spite of antibiotic prophylaxis (52). According to a RCOG systematic review and guideline, steroids do not increase the risk of infection in either mother or baby (15).

1.9.3 Home or outpatient management

The management of PPROM varies depending on the local guidelines, health care setting, the opinion of individual clinicians and protocols (53). Some maternity hospitals offer management of PPROM as an outpatient. Planned outpatient management is offered after a period of monitoring in hospital with administration of antibiotics and corticosteroids at least for 48 to 72 hours. Patients considered suitable for outpatient care include:

- Those living close to the hospital.

- Access to reliable transportation.

- No clinical evidence of intrauterine infection or antepartum haemorrhage

- Absence of contractions and cervical dilatation less than 4 cm.

The advantages of outpatient care may include:

- Greater convenience for patients and their families

- Reduced risk of thromboembolic diseases

- Reduced costs for health care providers

Beckmann and colleagues showed no difference in adverse perinatal and maternal outcomes in women who remain undelivered after 72 hours of PPROM either receiving hospital and/or outpatient care and did not show that prolonged hospitalisation is associated with a reduction in the risk of morbidity for mother and baby (48).

There is not enough evidence to make recommendations for outpatient or home management rather than expectant management (EM) in hospital in patients with PPROM. The outpatient management for PPROM must be restricted to specific patients and women should be able to take regular temperature recordings at home every day (15).

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There are two main reasons why outpatient management for PPROM is not recommended, namely an increased risk of chorioamnionitis and fetal distress (54).

The management of PPROM is dependent on the GA at the time of rupture of membranes (53), and in order to make a decision regarding the management of PPROM, the potential risks and benefits of immediate delivery (ID) against EM for each gestational age need to be weighed (51). ID would include a planned early birth by either induction of labour or caesarean section, while EM would be close monitoring of both fetus and mother till spontaneous labour or appearance of a complication that necessitate delivery (51). The main aim for EM is to prolong pregnancy and reduce gestational age dependent neonatal morbidity and infections (8).

1.9.4 Management options according to gestational age:

1.9.4.1 Patients with PPROM less than 24 weeks gestation

This is known as previable Premature Prelabour Rupture of Membranes (pPPROM). The incidence is less than 1% of all pregnancies but is associated with high perinatal morbidity and mortality. In the absence of infection, anhydramnios or fetal anomaly, women who experience pPPROM can be offered either termination of pregnancy or expectant management. Azria et al showed that perinatal risks after pPPROM remain higher whether women with pPPROM choose conservative management or termination of pregnancy (23). Kieffer et al found that there is no difference in neurological outcomes at 2 years in the very preterm premature rupture of membranes between 14 and 24 weeks gestation compared to those without ROM (26 to 36 born at similar GA (55).

1.9.4.2 Patients with PPROM between 24 and 34 weeks gestation

The first half of the third trimester is particularly troubling because of the competing risks of remaining undelivered versus the risks of iatrogenic prematurity following immediate delivery. The interventions for PPROM at this stage include the use of steroids, antibiotics, amnioinfusion and tocolytics and management can be expectant or planned early delivery(54). Expectant management is associated with increased risks of maternal and perinatal infections (neonatal sepsis and chorioamnionitis), oligohydramnios (associated with cord compression, pulmonary hypoplasia and bronchopulmonary dysplasia) and risk of still birth (placental abruption and cord accidents), while on the other hand, immediate delivery poses risks to the newborn because of iatrogenic prematurity that also vary across gestational ages (51). Al-Mandeel et al found that immediate delivery for PPROM at this gestation has no maternal or neonatal benefits (such as decreased risk of maternal infection either antenatal or postpartum) compared to expectant management. In fact, immediate delivery is associated with higher risk of neonatal deaths and increased the risks of caesarean section by 35% (51) .

1.9.4.2.1 Steroids

Betamethasone (BMZ) is preferred than dexamethasone due to slightly increased risk of periventricular leukomalacia associated with dexamethasone in children born prematurely (49). According to the RCOG clinical guideline, antenatal corticosteroid therapy in women with PPROM is beneficial between 24 to 34 weeks of gestation (15).

1.9.4.2.2 Antibiotics

The use of antibiotics in PPROM between 24 to 34 weeks gestation has been shown to have a significant improvement in short term maternal and neonatal morbidity including reduced

need for surfactant and oxygen therapy, prolongation of pregnancy, less risk of abnormal cerebral ultrasound and reduction in neonatal infection (53)(56)(14)(2). Cousens and associates showed that antibiotics for PPROM can reduce death due to sepsis by 39% and reduce complications of prematurity by 12% (2). The main role of antibiotics in PPROM is to prevent ascending infection or treat subclinical infection, thereby improving neonatal outcome (56).

The most common causative agents for intrauterine infection in PPROM are anaerobic , aerobic and mycoplasmas, thus broad spectrum antibiotics (erythromycin and ampicillin) are more beneficial in PPROM (8). The Oracle 1 trial showed that erythromycin when compared to placebo was associated with a reduction in chronic lung disease (decreased need for exogenous surfactant, neonatal ventilation or oxygen), and decreased major cerebral abnormalities as well as a reduction in the rate of positive neonatal cultures (14). Even though erythromycin the is most frequently used macrolide antibiotic for mycoplasma and bacterial infection during pregnancy, it has severe gastrointestinal side effects and poor oral bioavailability limit the clinical utility thereof (56). A clinical trial of an antibiotic regimen that used clarithromycin (a semi-synthetic macrolide antibiotic) showed that it may be an alternative worth considering with potentially beneficial effects compared to erythromycin in PPROM. The reasons are its better oral bioavailability, it is associated with a lesser degree of histological funicitis and better tissue penetration (e.g.to placenta) compared to erythromycin (56).

Yeung et al showed that penicillin is the drug of choice to treat group B Streptococcus infections, which remains as the most predominant organism causing early onset neonatal sepsis (GBS) in active carriers and erythromycin is less effective in treating GBS infections (16).

The ORACLE 1 trial also found that amoxicillin/clavulanic acid was associated with decreased uterine infection compared to erythromycin and placebo, but there was greater number of babies with suspected or proven necrotising enterocolitis in the amoxicillin/clavulanic acid group than in any no amoxicillin/clavulanic acid group and there wasn't any harm associated with erythromycin (14), therefore the use of amoxicillin/clavulanic acid is not recommended in this context.

1.9.4.2.3 Amnioinfusion

PPROM leads to oligohydramnios, thus placing the fetus at risk of umbilical cord compression and other complications such as pulmonary hypoplasia. Amnioinfusion has been described as a method of preventing such complications (15), but according to the PPROMEXIL III trial by van Teeffelen et al there was no evidence to support the use of amnioinfusion in the management of PPROM (57).

1.9.4.2.4 Sealing procedure for PPROM

The routine use of sealants is not currently recommended for treatment of second trimester oligohydramnios by PPROM due to lack of sufficient evidence to support its success rate and safety in a recent systematic review (5).

1.9.4.3 Patients with PPROM over 34 weeks gestation

The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend induction of labour (IOL) for PPROM after 34 weeks gestation. The RCOG guidelines also

recommends delivery after 34 weeks gestation but those who are managed expectantly beyond 34 weeks should be counselled regarding the risk of CAM and presumed decreased risk of neonatal respiratory complications, admission for neonatal intensive care and caesarean section (58). According to the PPROMEXIL II trial, van de Ham and associates showed that for pregnancies complicated by PPROM after 34 weeks of gestation, IOL does not reduce the incidence of neonatal sepsis nor did it influence the rates of caesarean section and respiratory distress compared to expectant management. However, IOL increased the risk of hyperbilirubinemia, hypoglycaemia and the use of epidural analgesia during labour (59).

An evidence based clinical protocol was developed and implemented in 2012 at Tygerberg Hospital for investigation and management of PPROM, based on the best available international guidelines and evidence from randomised controlled trials (60). Gaps often exists between clinical guidelines and the eventual clinical practice (61), therefore the development of a specific protocol or tool that specifies exact steps and actions to be taken can assist in guideline implementation (62). However, there may be large gaps between the known effective practices and what is actually done in real life and in clinical practice often performed under less than ideal circumstances (63).

Fidelity in research refers to the extent that the study team complies with the study protocol and is different to *adherence*, which refers to the behaviours of the participants (64). *Implementation* (or *intervention*) *fidelity* can be described as the degree to which a specific intervention is delivered as prescribed or intended during clinical practice (65). The same principles apply to interventions aimed at improving clinical care and any clinical protocol will only be as effective as the clinical personnel administering the critical steps. There are not many examples of intervention fidelity in clinical practice neither does a literature search readily identify tools or models that can be used.

The method employed in this study was to evaluate each component of the protocol based on written evidence in the clinical notes. For each component, a dichotomous question was developed to provide a Yes/No answer. This is further described in the methods section.

The two cardinal questions that arise with this type of intervention research is whether the intervention is applied as prescribed and whether it makes a difference to clinical outcome. The latter can only be measured when there is a control group without the specific intervention (or historical pre-protocol outcome data is available). Very large sample sizes will be needed to measure any difference in clinical outcome. But the evidence and comparative studies are already available and distilled into a protocol. The implementation part is more related to the external validity of all the guidelines. The intention is therefore not to measure the impact of the protocol on clinical outcome, but to focus on the correct implementation and ways of improving the care. This in turn may improve the quality of care delivered to women with PPROM.

2. Objective and aims

2.1 Objective

- The objective of this study was to evaluate the quality of care delivered to women undergoing inpatient management with PPROM by measuring intervention fidelity to a recently instituted hospital protocol.

2.2 Aims

- To describe the characteristics of women admitted for conservative management of PPROM.
- To describe the practices of the clinical personnel during management of women with PPROM during the pre-admission phase as well as during the in-patient period.
- To measure intervention fidelity to the new protocol.
- To determine the impact of the protocol on hospital stay (bed occupancy rate).
- To determine pregnancy outcome and PPROM-linked mortality.

3. Methods

3.1 Study design

This was a prospective population-based observational study.

3.2 Setting and study population

The study group were all women between 24 and 34 weeks of gestation, admitted for conservative management of confirmed PPROM between 1 February 2014 and 31 January 2015. Tygerberg hospital is a referral hospital for all women with complications requiring specialist attention. The greater catchment (referral) area is a geographic health district in Cape Town called Metro East (consisting of 14 sub-councils) with a population of 2 416 560 (2011 census). Within Metro East there are 3 large district hospitals and 8 midwife obstetric units (MOU) that refer women to Tygerberg according to a standardised protocol. This regionalisation of care is driven by a set of protocols and care is standardised across the platform.

The PPROM protocol was workshopped with all clinicians before implementation and was readily available (printed copies in all clinical areas and electronic version on the departmental website). A copy of the protocol is attached as Appendix I.

3.3 Inclusion criteria

The diagnosis of rupture of membranes was made on clinical grounds as per hospital protocol by a combination of convincing history and confirmed by speculum examination (pooling of liquor in the posterior fornix). When the diagnosis was doubtful, pH changes in vaginal fluid was determined using litmus paper and fluid was examined under a microscope for ferning. If still doubtful, women were admitted for sanitary pad check for 24 hours followed by amniotic fluid determination on ultrasound (amniotic fluid index >5 or deepest pool >3 cm regarded as

normal). If pads were dry and amniotic fluid volume normal, they were discharged and not entered into the cohort. Conservative management (inpatient treatment) included bed rest, antibiotic and corticosteroid administration, tocolysis if in labour before steroid maturity (within 48 hours after PPROM). Women remained in hospital until 34 weeks or spontaneous onset of labour. If not delivered by 34 weeks, they were induced according to standard protocols for induction of labour.

3.4 Exclusion criteria

Women who were in active labour on presentation, multiple pregnancies, clinical signs of chorio-amnionitis, fetal compromise, cord prolapse, fetal death, gestation >34 weeks and women who declined conservative management of PPROM were excluded. Clinicians managing women were not aware of the audit.

3.5 Measurement of intervention fidelity

A set of 23 questions were developed to measure fidelity to each of the 23 critical components of the protocol. Overall mean fidelity to the protocol was calculated as the number of interventions fulfilled/23 (the total number of interventions recorded). There were 15 interventions related to pre-admission selection and 8 related to conservative management as inpatient. The tool is available as Appendix II.

3.6 Data collection

Data collection was done retrospectively, after discharge of the baby from the hospital, to minimise observer effects. The charts of all patients (n=353) were retrieved from the online TBH records system, Enterprise Content Management (ECM) and data extracted by the principal investigator. Baseline delivery data was obtained from routinely collected hospital and regional data.

The following maternal characteristics were collected: date of first antenatal visit, level of care, maternal age. For obstetric history, data were collected on gravidity and parity, previous surgery on the genital tract or uterus including caesarean section and cervical cerclage, previous preterm labour or PPROM and current obstetric history. The medical history, pre-pregnancy body mass index (BMI), HIV, syphilis, rhesus status and lifestyle factors (smoking, alcohol, recreational drugs) were obtained from the first antenatal visit notes.

Clinical data on the date admitted with PPROM, confirmatory tests for SROM, maternal vital signs on admission, urine analysis, haemoglobin value, uterine activity, ultrasound on admission and indication for ultrasound, baseline fetal monitoring (cardiotocography CTG) and midstream urine culture and sensitivity were obtained from the clinical notes and laboratory reports. The prescription chart and nursing notes was analysed to obtain data regarding nursing instructions, antibiotic prescription, daily fetal movement monitoring and CTG, corticosteroids, tocolysis and any other drugs or agents.

The clinical notes were used to assess documentation of counselling, date patient discharged from protocol and reason and any complications arising during the hospital stay. The hospital patient information system was used to determine length of stay in hospital for mother and baby. The delivery report was used to obtain data on the mode of delivery, method of delivery, maternal complications during delivery and the date of delivery. The neonatal folder was analysed for birth weight, Apgar scores (1 and 5 minutes), outcome of baby and any complications. Maternal mortality was defined as any maternal death during pregnancy or within 42 days after delivery; a neonatal death as any death occurring after delivery and before 7 days of life and stillbirth any death after 22 weeks but before delivery.

3.7 Data analysis plan

Demographic, clinical and outcome data were entered in an Excel spread sheet. Patient identity was delinked from the data sheet and sequential numbers were allocated to individual patients. Data analysis was done using STATA 14 (StataCorp LP, USA).

3.8 Ethical considerations

Consent to perform the study was obtained from the Health and Research Ethics Committee of Stellenbosch University as part of a larger study into patient outcomes at Tygerberg Hospital (S12/09/240). A waiver of patient consent was obtained as data was collected retrospectively, after discharge of the patient.

4. Results

There were 34 948 deliveries during the study period in the metro east geographical region with a population-based caesarean section rate of 26.3%. Of these, 721 were stillbirths; 285 in the 500-999g birthweight group and 436 weighed 1000g or more. Of the 34 227 live births, 149 babies died within 7 days of birth and 35 were late neonatal deaths. PPROM was the primary (obstetric) cause of death in 1.7% of perinatal deaths in the population. Only 5 of these deaths were reported outside of Tygerberg hospital (all stillbirths). Tygerberg is the only referral hospital for women with ROM prior to 34 weeks where conservative management is appropriate. On evidence of this data, it can be assumed that most women with PPROM would have been referred and managed appropriately at Tygerberg hospital and included in this survey.

Of all the deliveries in Metro East, 8436 delivered at Tygerberg hospital with a CS rate of 47.35%. There were 419 multiple pregnancies. During the study period 353 women were referred to Tygerberg for suspected PPROM. After excluding those who delivered on arrival and those without evidence of PPROM, n=98 women qualified for conservative management. The cumulative incidence of PPROM during this study period was 2.86 per 1000 deliveries. The syphilis prevalence amongst perinatal deaths was 10/1000.

The baseline demographic and clinical characteristics of the participants are shown in Table I.

Table 1- Baseline demographic characteristics

	Number	Percentage
Age		
<19 years	17	17,3
19-37 years	75	76,5
>37 years	6	6,1
Racial ethnic group		
African	56	57,1
Mixed ancestry	42	42,9
Gravidity		
1	31	31,6
2-5	60	61,2
>5	7	7,1
Parity		
0	34	34,7
1-5	60	61,2
>5	4	4,1
Body Mass Index (BMI)		
<18.5 (underweight)	5	5,1
18,5-24,9 (normal weight)	45	45,9
25-29,9 (obese)	23	23,5
>30 (morbidly obese)	25	25,5

The mean age on admission was 26.3 years (range 17-42 years) with most patients in the 19-37-year-old group. The mean BMI was 27.4 kg/m^2 with a range of 17.1-47.7 kg/m^2. Almost half (49%) of all women admitted were in the obese (BMI ≥25 kg/m^2) category.

The lifestyle habits of the patients are shown in Figure 2. More than 35% of the women were smoking during the pregnancy. Drugs and circumstance refer to the abuse of any illicit drugs.

Figure 2- Lifestyle habits of the women admitted to the study.
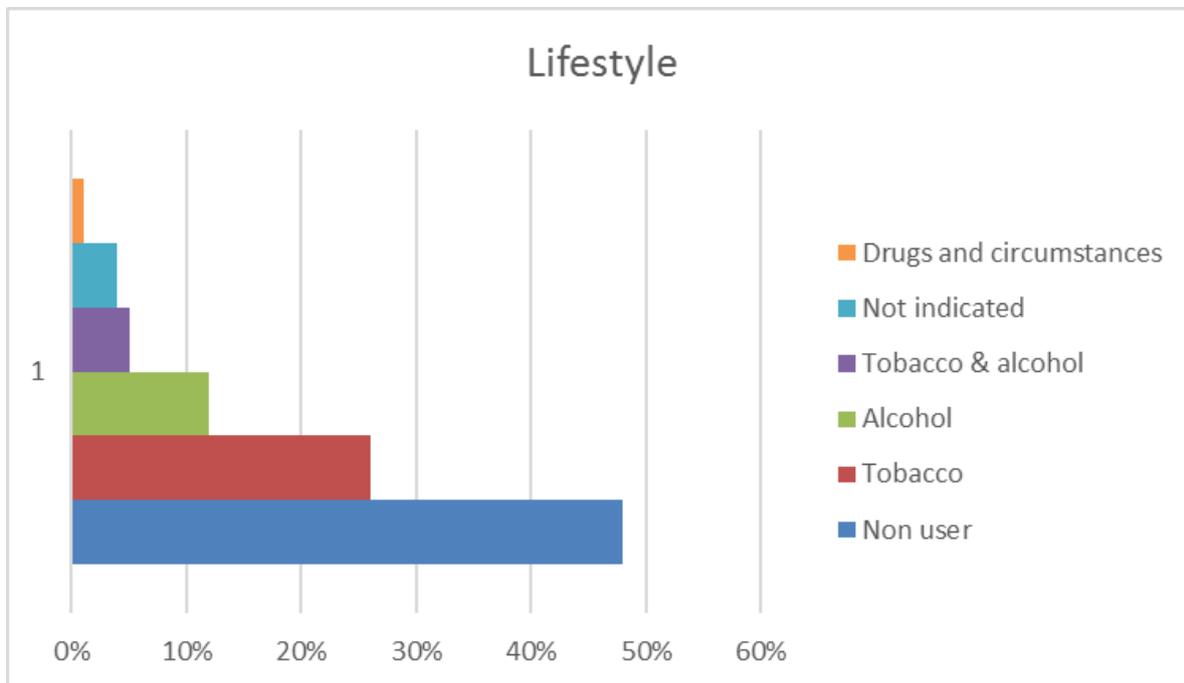
The method of diagnosing SROM is shown in Figure 3. In most women the diagnosis was made with a pH change in the vaginal fluid using Litmus paper (almost 60%).

Figure 3. Method of diagnosis of SROM.
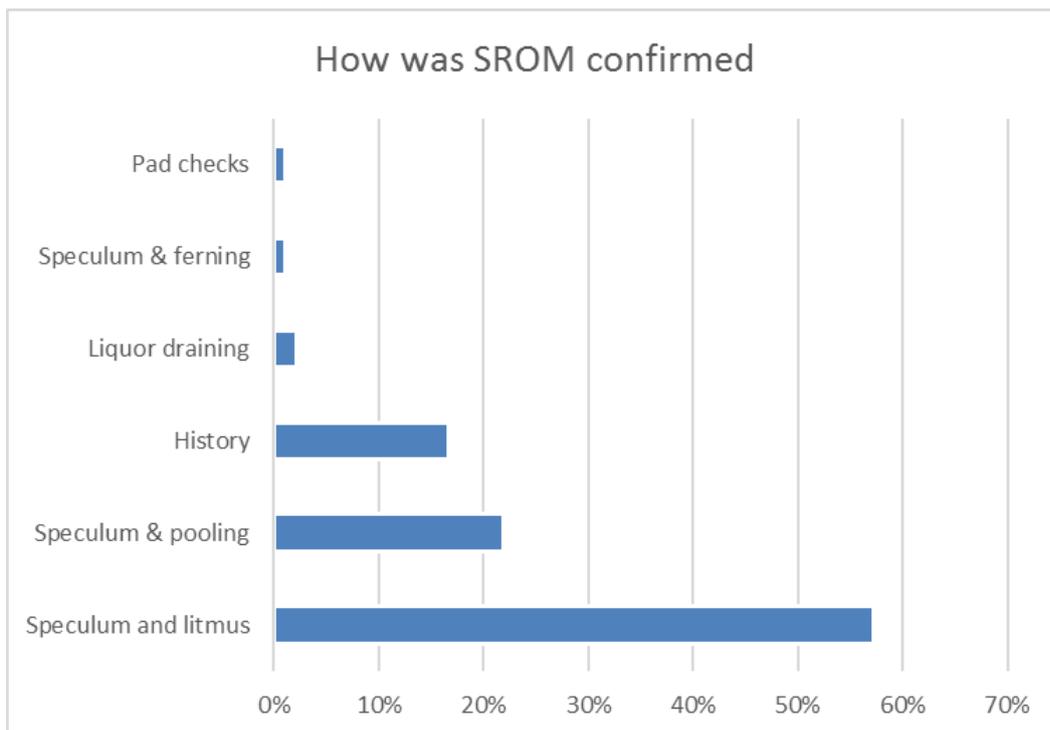
Tocolysis was indicated in 33 (34.5%) in women. The agents used for tocolysis are shown in Figure 4

Figure 4. Agents used for tocolysis when indicated.
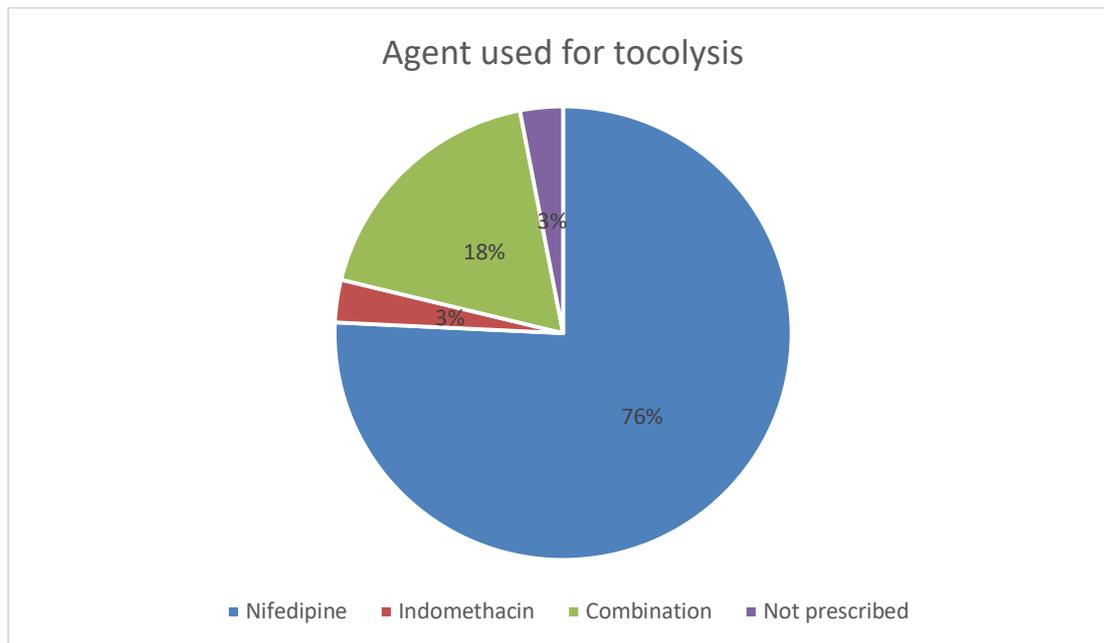
Eighteen percent of women had a previous history of miscarriage and 11% a history of previous preterm labour. This is shown in Figure 5.

Figure 5. Previous obstetric history.
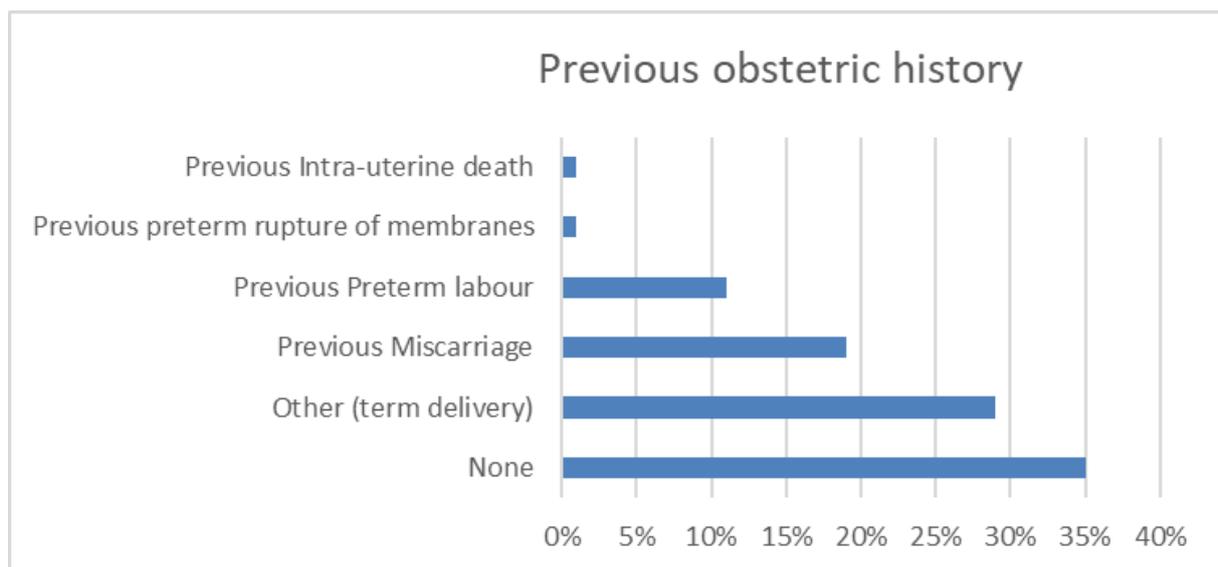
About 18% of women had previous miscarriage and only 11% had previous preterm labour.

The current obstetric history is shown in Figure 6. More than 20% of women already had symptoms or signs of preterm labour earlier in the index pregnancy.

Figure 6. Current obstetric history.
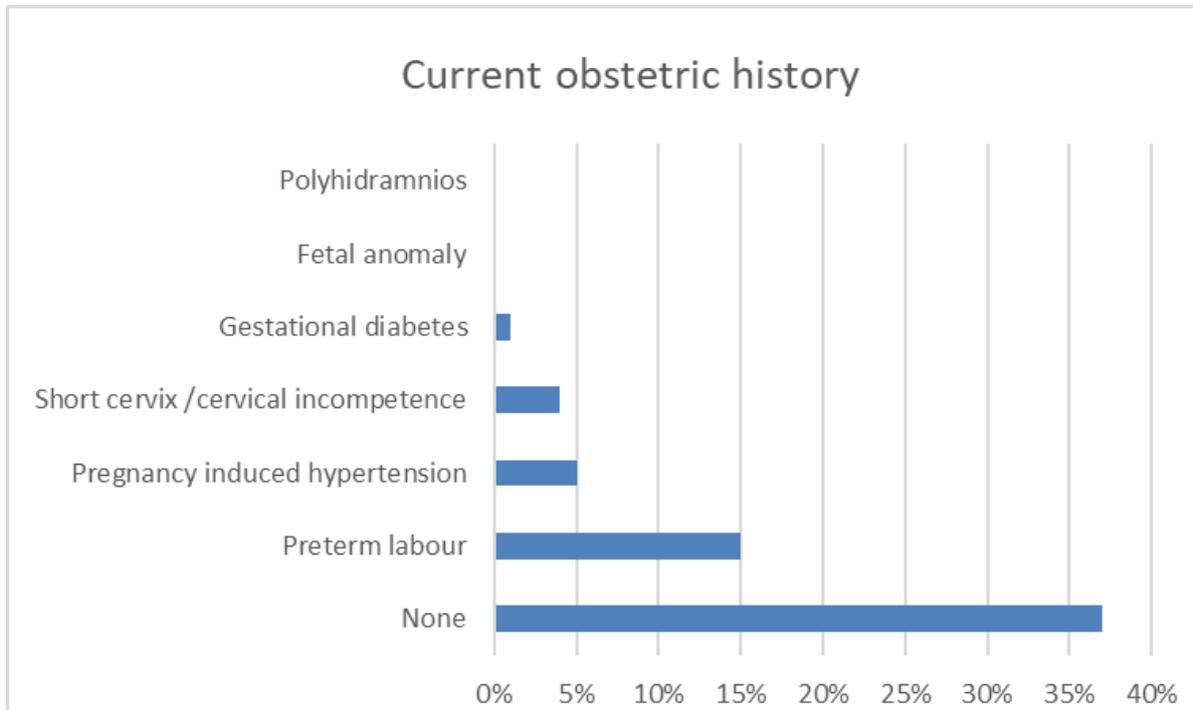
Most women (almost 80%) were healthy at the time of entry to the study. This is shown in Figure 7.

Figure 7. Medical history of women admitted with PPROM.

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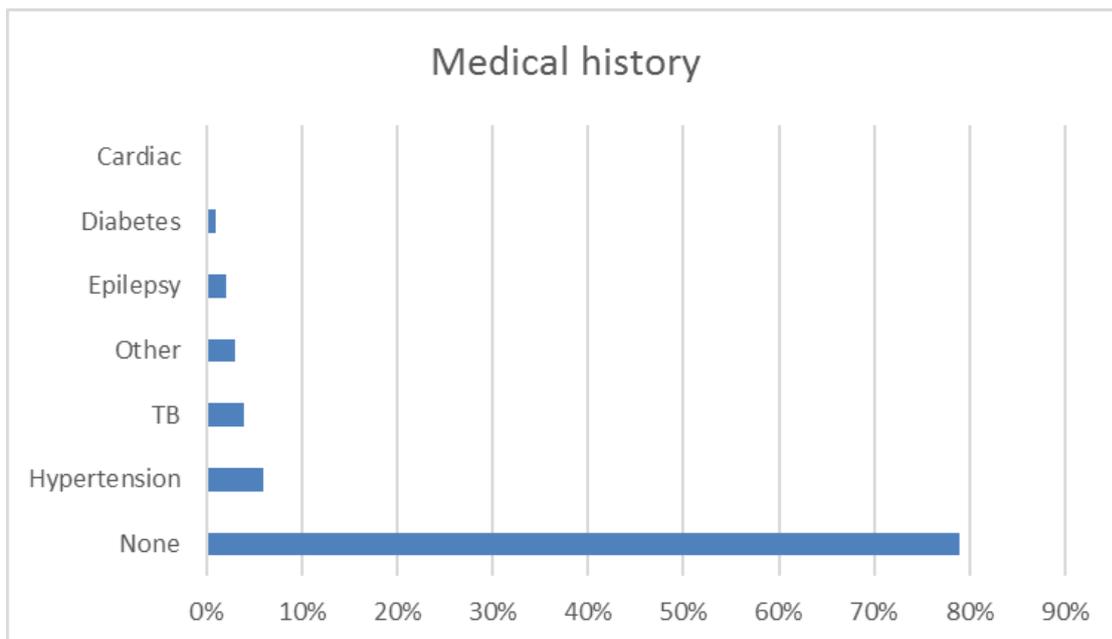
Most women went into spontaneous labour before 34 completed weeks. The reason for discharge from the protocol is shown in Figure 8. Less than 15% reached 34 weeks with conservative management.

Figure 8. Reasons for discharge from the protocol.
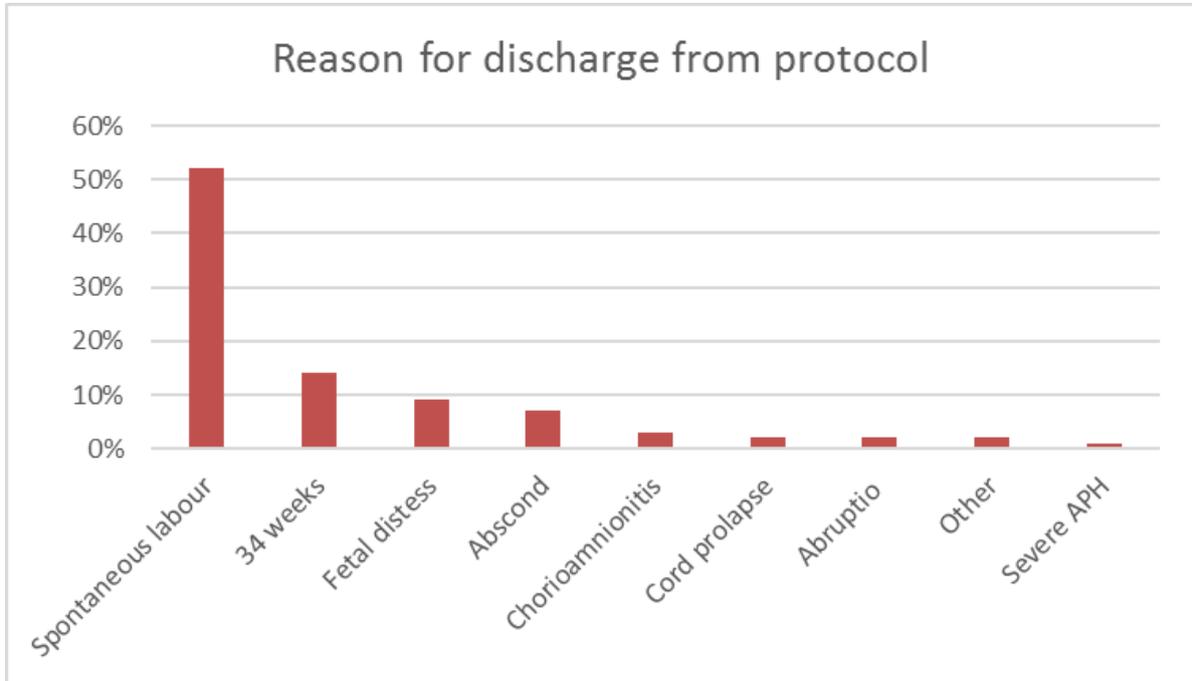
The mode of delivery is shown in Figure 8. Twenty-six percent of women were delivered by caesarean section.

Figure 9. Mode of eventual delivery.

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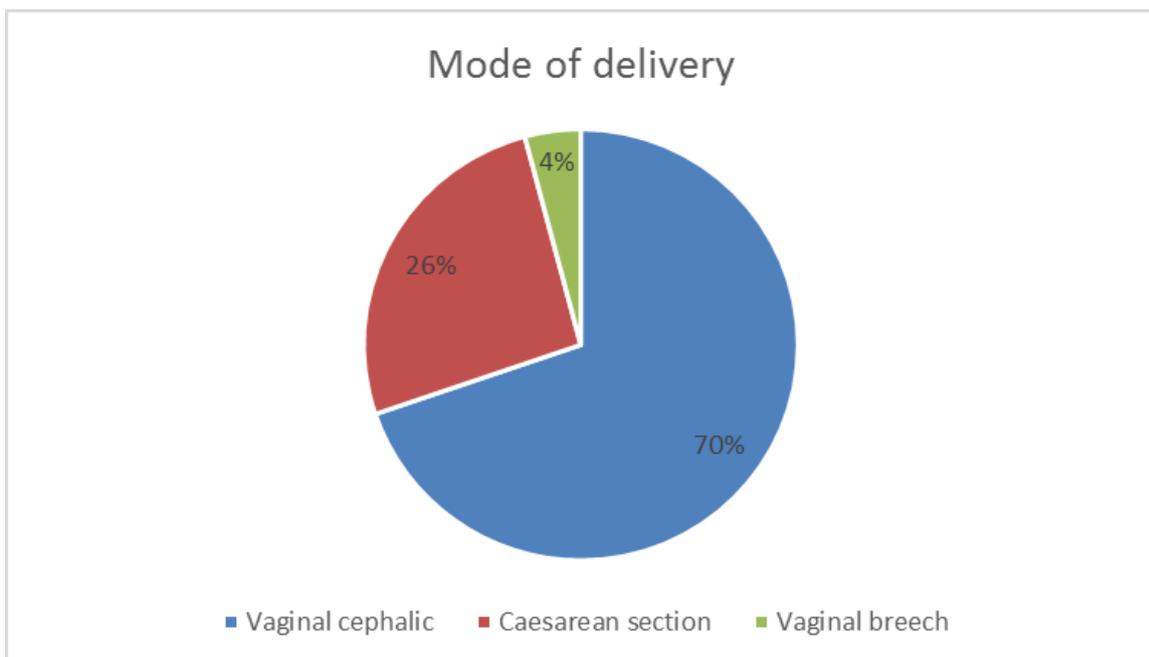
Half of all the Caesarean sections were for some form of fetal compromise during labour. Fourteen percent of caesarean sections were done for undiagnosed breech. This is shown in Figure 10.

Figure 10: Indications for caesarean section
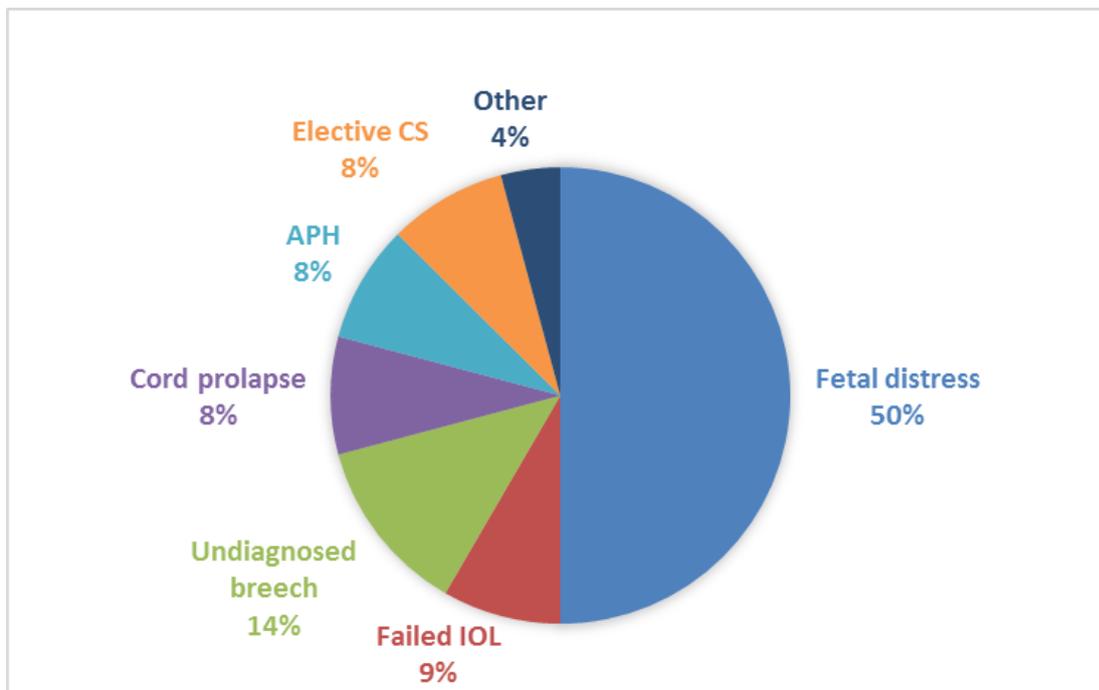
The mean pre-admission fidelity to protocol was 51.3% and the mean inpatient fidelity was 45.8%, which was not significantly less (p=0.43). Overall, fidelity to all facets of the intervention protocol was less than 50%. This is shown in Figure 11.

Figure 11. Overall protocol fidelity as measured by the audit.
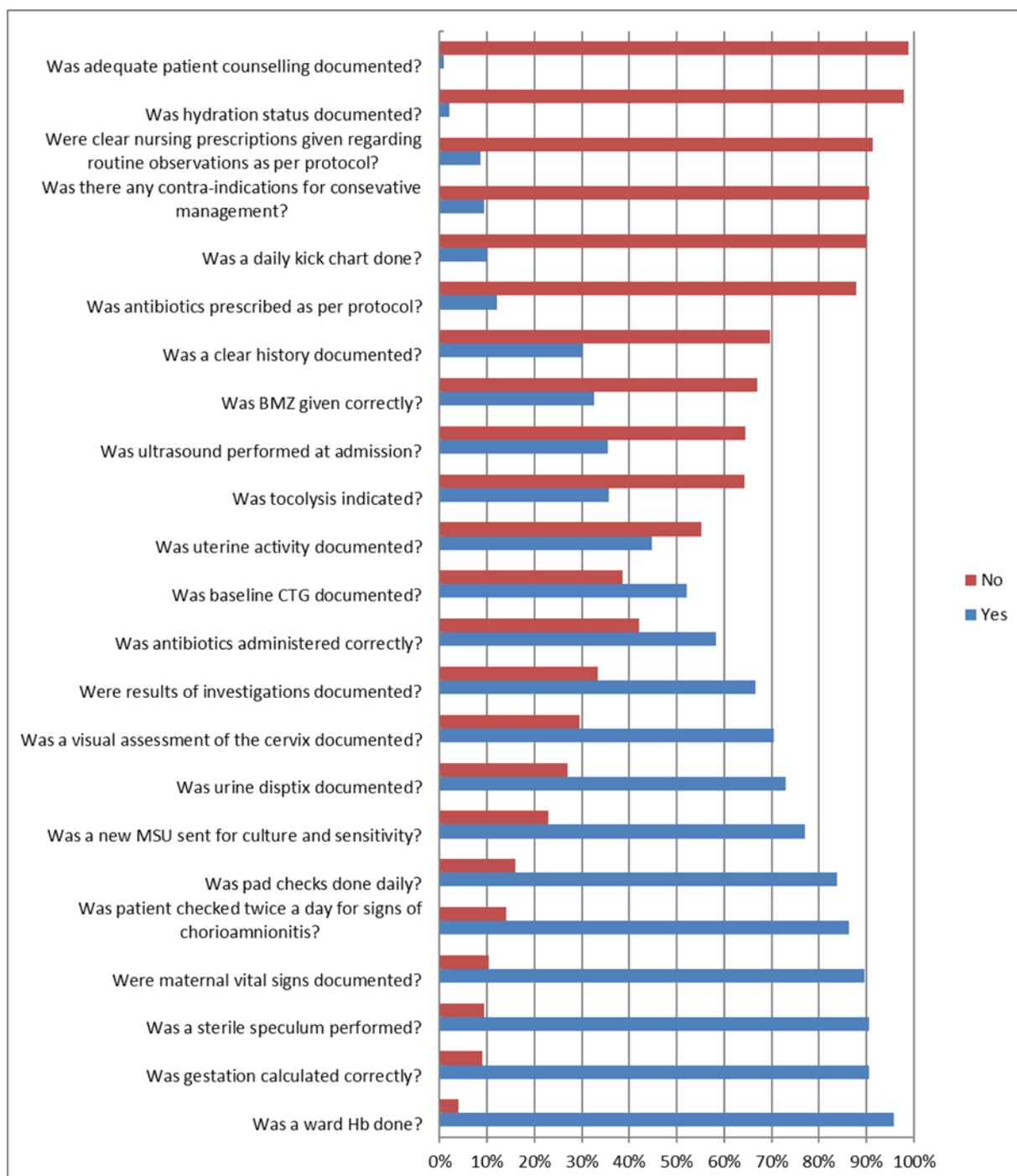
In more than 90% of women, no adequate counselling was documented. Clear nursing prescriptions were not given in 90% of patients as per protocol. More than 65% of patients were not given BMZ correctly. Close to 60% of women were given antibiotics correctly. About 86% of women were checked for signs of chorioamnionitis twice a day.

Maternal outcomes:

None of the women had any severe maternal complications during the antenatal stay or delivery.

Most babies were admitted to High care. There were 5 ICU admissions and 6 deaths. This is shown in Figure 12.

Figure 12. Neonatal outcome.
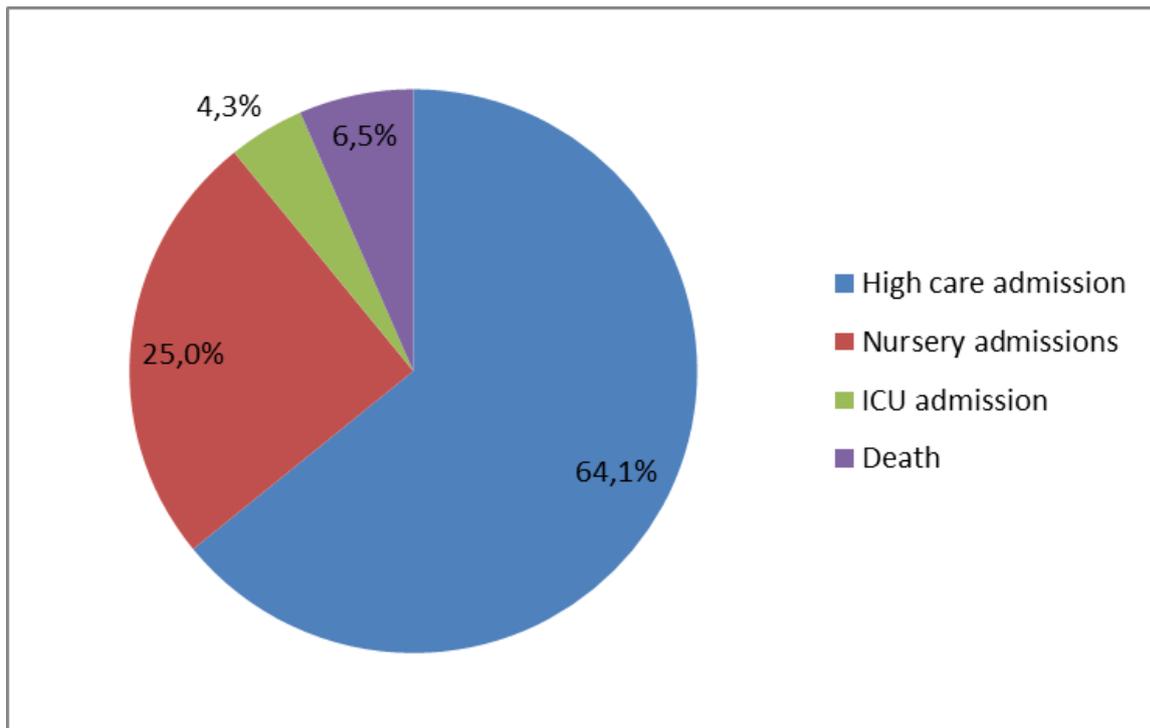
Birthweights according to the accurate gestation (based on early ultrasound where available) were plotted on a chart using the 90th, 10th and 3rd centiles for growth according to the INTERGROWTH (66) standards, which is in use at Tygerberg Hospital as the preferred standard to assess for small-for-gestational age babies (SGA). There were 18 SGA babies in the cohort, of which 10 was severely small (below the 3rd centile). This is shown graphically in Figure 13, with weight on the Y axis and gestation on the X axis and the centiles shown as P3, P10 and P90. The median birth weight was 1690g (range 750g-2990g). The median gestation at delivery was 31 weeks and 4 days (range 24 weeks 5 days to 35 weeks 1 day).

Figure 13. Birth weight according to gestation at delivery.
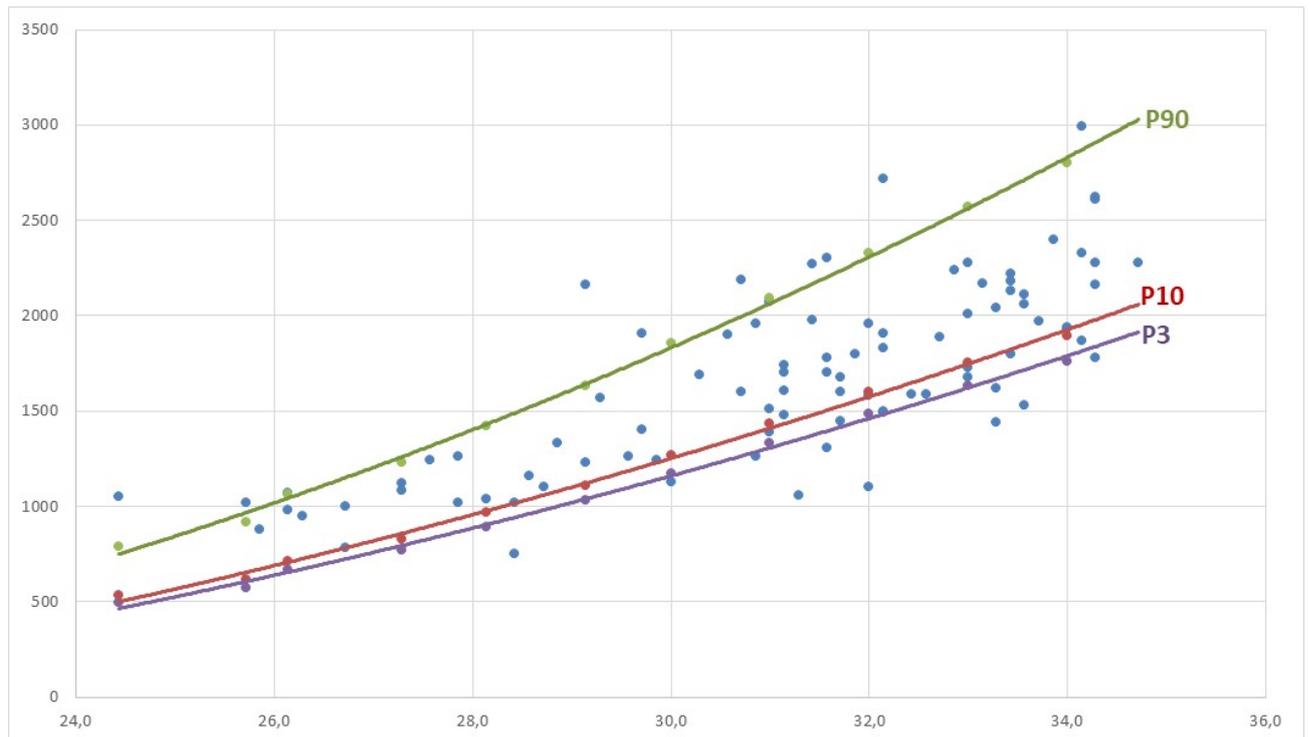
Women stayed a median of 4 days on the protocol (admission to delivery) with a range of 0-29 days. The total length of stay of mothers (from admission to discharge from hospital) was a median of 6 days (ranging from 1- 63 days) and most these mothers stayed in hospital post-delivery due to their babies admitted either in ICU or high care. Seven of the women refused hospital management and 6 of them came back in spontaneous labour and had normal vaginal delivery with no maternal complications and the babies stayed a maximum of 6 days in hospital with good outcomes; 1 case had an elective repeat CS.

Babies were admitted for a median of 8 days after delivery (range 0 to 188 days). There were 6 babies who died, mostly from severe prematurity. Sixteen babies had a low 1-minute Apgar score of <7 and six of them died and 10 of these babies had a prolonged stay in hospital. Sixty babies suffered from neonatal jaundice. Fourty-one babies had HMD/RDS. Seven babies had severe sepsis and two of them died from other complications of prematurity.

Only three babies had NEC. They were all below the gestation of 30 weeks. Two of them were given BMZ correctly and one of them BMZ was given 18 hours apart instead of 24 hours. Seven babies had feeding intolerance and 6 of them had a prolonged stay in hospital and all had a weight of below 1200g. Four babies suffered from PDA and two of them were admitted in ICU and had a prolonged stay (100 and 72 days, born at 28w4d and 31w 2d respectively). The other 2 were admitted in High care (37 and 27 days, born at 30w0d and 29w1d respectively).

Regarding the six neonatal deaths, there were 3 unexplained intrauterine deaths with no clear evidence of clinical chorioamnionitis or abruptio placenta; the other 3 were neonatal death after 15, 25 and 50 days in hospital post-delivery. These were associated with complications of prematurity.

5. Discussion

Although the sample is small, the results of this retrospective audit enabled an assessment of the actual inpatient management of PPROM at Tygerberg Hospital to see if this complied with the recommended protocol for PPROM that was implemented in 2012. In terms of clinical data and outcomes, the first striking finding is that most cases of PPROM occurred in women without a previous history of preterm labour or PPROM. They were also healthy with no underlying medical condition. The implication is that these women will be attending antenatal care at community clinics and it is important that basic antenatal care providers are regularly updated on the diagnosis and correct initial management before referral. Nimrodi and colleagues investigated a hypothesis in a similar group of low risk women, speculating that pre-existing cervical inflammation may lead to PPROM; however in this population-based cohort there was no difference in clinical outcome in the group with inflammation and the group without (67). Until there is an easily identifiable risk factor for PPROM, routine care will have to include information on this specific danger sign of pregnancy.

It is important to note that in many women there were a prior alert in the current pregnancy (mostly a prior episode of preterm labour). These women therefor need to stay at a more specialised level of antenatal care and be well informed. A randomised trial from India in a similar low-risk population showed that routine cervical length screening did not reduce the risk of pre-term labour, therefore increase clinical vigilance remains the only current standard of care (68).

More than half of women in the study were obese; this is a known risk factor for PPROM and in the Metro East regionalised perinatal care system a BMI of >40kg/m^2 is a reason for referral for specialist care. A recent study showed that even amongst women managed conservatively for PPROM, maternal obesity was an independent risk factor for chorioamnionitis with a hazard ratio of HR 1.6 (95%CI 1.1–2.1, p = 0.008) (69). Future protocols of conservative management

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of PPROM may include earlier elective delivery for obese women and this is an area that needs further research in the TBH population.

The study results regarding neonatal outcomes (complications of prematurity and prolonged hospital stay) is consistent with what has been found in the literature as summarised in the introduction. Although infection is a major trigger for PPROM, sepsis is also the most important cause of morbidity in the premature infant and therefor premature deliveries in women with PPROM should be avoided to decrease prematurity related outcomes. This is also the conclusion of a recent study to assess the predictors of outcome in terms of length of stay and survival of neonates from women with PPROM (70). Even this may be difficult, as only 15% of women made it to 34 weeks in the current study.

It is surprising that 14% of CS were done for undiagnosed breech presentation in labour. These are patients managed in a setting where they should receive daily abdominal examinations for signs of infection. Health care workers should be reminded to note the presentation at the daily examination and be prepared for management of a breech presentation and the associated risks (including cord prolapse).

The main reason for Caesarean delivery was fetal distress. Babies from mothers with PPROM are already compromised babies at risk for antepartum and intrapartum fetal heart rate abnormalities, so this was not an unexpected finding. Davis and colleagues investigated continuous fetal monitoring for PPROM before the onset of labour and found that abnormal heart rate tracings are already present in a significant percentage of women (71). The current hospital protocol recommends only one CTG per day and the importance (and feasibility) of a more frequent schedule needs to be investigated. A study measuring fidelity to a protocol of continuous fetal monitoring in women with PPROM found that a significant proportion (28.3%) of CTGs were not recorded as ordered (72). Fetal monitoring can also predict histological

chorioamnionitis- a study from France showed that decreased variation in the fetal heart rate pattern was associated with chorioamnionitis, especially in the last 24 hours before delivery (73).

Although most babies were appropriately grown for their gestation, 18 babies were smaller than the 10th centile for birth weight according to their accurate gestation. These findings were not detected before delivery, and a special effort should be made to diagnose the SGA babies in the PPROM cohort. They are more at risk- SGA babies mothers with PPROM has an increased risk for severe neonatal morbidity, early childhood death and moderate or severe cerebral palsy (74). Since the study was done, a new protocol for management of SGA babies was introduced at Tygerberg Hospital. A large population-based study in women with PPROM found that the risk of cognitive impairment during childhood was greatest when the period between rupture and delivery was less than three days (75). This is an important finding, as the median number of days gained in the current study was only 4 days.

In terms of quality of care, the lack of adequate counselling (as documented in the folder) in 90% of patients admitted with PPROM is a cause of concern. It is the responsibility of the admitting and treating health car practitioner to counsel parents about PPROM as it is associated with poor adverse perinatal outcomes and prolonged stay for both mother and baby. There is therefore a need to educate health care providers in the facility on the multiple management options and interventions and to enhance communication skills. A program of training and monitoring of providers ensure implementation fidelity in clinical trials in other settings and that knowledge can be used to ensure fidelity in this hospital setting as well (76). A simple patient information leaflet can also be developed to assist with information. In the literature, barriers to implementation fidelity include time constraints in daily practice, difficulties with patient selection and incompleteness of medical files (77).

The tool developed here can be used (or adapted for other clinical scenarios) for any quick survey of the quality of care delivered to a specific patient group. The tool is available as an Excel document that generates the findings automatically in descending order of importance as answered. There is a growing body of evidence on fidelity scales and performance measures as tools to support quality assurance in a variety of health care settings (78). It may also be better to focus on a tool design that explore and explain variation in implementation fidelity rather than aiming to control for that variation (79).

6. Conclusion

Based on the data and discussion presented here, the management protocol can be updated to include the clinical aspects that was identified during the audit (including the clinical importance of obesity, checking the presentation daily to exclude undiagnosed breech, and careful assessment and more frequent fetal heart rate tracings).

A further recommendation is that the data obtained from this study be used to develop a patient counselling and information leaflet. Important factors to include will be the signs and symptoms of infection, the risk for premature delivery, and the 26% risk for CS, the prolonged hospital stay for both mother and baby and the risk of adverse outcome of the baby.

Regarding intervention fidelity, the tool is now available for use and can be refined and adapted to monitor implementation of the recommendations from this study and the effect this has on clinical care and quality of care.

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Appendix I- Protocol

TYGERBERG HOSPITAL
Department of Obstetrics and Gynaecology: General Specialist Services

PROTOCOL FOR THE ACUTE MANAGEMENT OF
SPONTANEOUS PRETERM PRELABOUR RUPTURE OF MEMBRANES

A. DEFINITIONS

Preterm Prelabour Rupture of Membranes:

 • The **spontaneous** rupture of fetal membranes before labour and prior to 37 completed weeks of gestations with:

   ☑ **Preterm** defined as after a gestation of **24w0d** and before **37w0d**.

   ☑ **Prelabour** defined as at least 1h before the onset of labour

Rupture of membranes determined by:

 • There is no clear '**gold standard**' test for ROM but a composite of the 4 following elements can be used:

   ☑ Documented **clear convincing history**

   ☑ Documented **clinical observation** of amniotic fluid: **pooling in the posterior fornix** or clear fluid **draining from the cervical os**

   ☑ Documented **alkaline test** with litmus paper (blue litmus stays blue)

   ☑ Documented **positive fernlike pattern (arborization)** on microscopy

B. COMPLICATIONS OF PRETERM PRELABOUR RUPTURE OF MEMBRANES

Preterm birth with associated prematurity including neonatal respiratory distress syndrome

Cord compression / cord prolapse

Fetal malpresentations

Chorioamnionitis

Antepartum fetal death

Abruptio placentae

Post partum endometritis / sepsis

Post partum hemorrhage

Retained Placenta

NB! *For the purpose of the protocol viability [for fetal monitoring with CTG] will be defined as-*

__Sure__ gestation of 27w0d __OR__ if the gestation is __unsure__ an EFW of 800g

---

1

C.   MANAGEMENT: INITIAL ASSESSMENT AND WORK-UP OF PPROM

1.   General assessment:

1.1.   Obtain a clear history of any symptoms of rupture of membranes, including predisposing risk factors for preterm prelabour rupture of membranes.

1.2.   Check antenatal card for MSU, HIV, Syphilis results and normal detail scan.

1.3.   Ensure correct gestation (Sure gestation = early ultrasound ± Dates / SF)

    To enable correct management in _Section F_

NB!   If patient is **unbooked** or **lost her card**:

  • Check for results on the computer, if not available do rapid HIV, Rh and Syphilis tests.

  • Request registrar on call to do basic scan, exclude gross abnormality and get EFW

    (Use the complete basic scan report form supplied)

 ! But do not delay management while waiting for the above !

1.4.   General examination

    1.4.1. Maternal vital signs, urine dipstick, including hydration status

    1.4.2. Asses uterine activity by abdominal palpation

1.5.   Consider ultrasound if gestational age, placental location, fetal presentation is unknown

1.6.   Obtain baseline CTG [if <u>sure</u> gestation ≥ 27w0d or if <u>unsure</u> gestation an EFW of ≥ 800g]

   • If pathological CTG – Do intra-uterine resuscitation according to protocol and if no recovery, immediately prepare patient for Caesarean Section and inform the registrar in charge.

2.   Perform sterile speculum examination.

2.1.   Exclude cord prolapse and take sample for wet mount smear.

   • If cord prolapse is present follow protocol for cord prolapse

2.2.   Document any evidence of ruptured membranes –

   • The presence of a pool of liquor in the posterior fornix is diagnostic of ROM

   • If doubtful, observe draining of liquor from cervical canal after coughing, confirm rupture with litmus paper or with microscopy
     [Beware of stress urinary incontinence in pregnancy!]

   • If still in doubt and there is a clear history refer to _Section D._

2.3.   Visually asses if the cervix is already dilated (**do NOT do digital examination**)

2.4.   If no evidence of rupture of membranes – Then either

   • Admit for observation (_see Section D_)

   • Discharge with advice on rupture of membranes, preterm labour and infection signs and symptoms.

2

3. **Digital cervical assessment should never be done in suspected or confirmed PPROM unless a clear decision for delivery has already been taken and -**

   There is established labour -
   - With persistent 3 strong contractions per 10min
   - Head ≤ 2/5 above pelvic brim

   ! One inadvertent vaginal examination should not exclude further conservative management !

4. **Side-room and special investigation:**
   4.1. Ward Hb (if no recent Hb on record for last 2 weeks)
   4.2. Mid stream urine specimen for culture and sensitivity

D. MANAGEMENT: IF NO CLINICAL EVIDENCE OF ROM BUT HIGHLY SUSPICIOUS HISTORY / ↓ AFI

1. **Admit patient to antenatal ward for:**
   1.1. Routine observations (with 6 hourly temperature, pulse and respiratory rate) and daily CTGs if viable.
   1.2. Monitor for signs of chorioamnionitis twice daily:
      - Maternal fever (>37.8°C), tachycardia (>120bpm), uterine tenderness, foul / purulent amniotic fluid or vaginal discharge
      - Fetal tachycardia (>160bpm)
   1.3. Daily kick charts
   1.4. Pad checks – if wet
      - Redo speculum (after a period of bed rest) to look for clinical signs and symptoms suggestive of ROM.

NB! If any signs of **chorioamnionitis, abruptio or fetal distress** then the patient should be delivered !

2. If **ROM confirmed** then follow protocol for confirmed PPROM
3. If **PTL confirmed** then follow protocol for PTL
4. If no ROM confirmed and no signs of chorioamnionitis after 24hrs then consider:
   4.1. Confirm normal AFI [AFI of > 8]
   4.2. Consider patient for discharge with a follow up at High Risk clinic in 1 week.
   4.3. Give adequate counselling on possible signs and symptoms of ROM / PTL and chorioamnionitis

3

E. **MANAGEMENT: CONSERVATIVE MANAGEMENT OF PPROM**

1. **Indications**

    PREMATURITY REMAINS THE COMMONEST CAUSE OF NEONATAL DEATH RESULTING
    FROM PRETERM RUPTURE OF THE MEMBRANES

2. **Absolute contraindications for conservative management / Indication for delivery:**

    2.1. Gestation of ≥ 34w0d or <24w0d

    2.2. Intrauterine death

    2.3. Severe / lethal fetal anomaly (In consultation with Fetal Medicine Unit)

    2.4. Suspicious / Pathological CTG

    2.5. Clinical suspicion of chorioamnionitis

    2.6. Severe maternal disease

    2.7. Severe intra-uterine growth restriction (< 3rd percentile)

3. **Relative Contraindications for conservative management:**

    (To be assessed and discussed with your Consultant)

    3.1. Antepartum haemorrhage of unknown cause

    3.2. HIV positive patients / Immunocompromised patients

4. **High risk patients for chorioamnionitis**

    4.1. Preterm rupture of membranes

    4.2. Prolonged rupture of membranes (> 24hours)

    4.3. Recent history of active genito-urinary infections

    4.4. HIV positive patients

    4.5. Diabetic Patients

5. **Admit patient to antenatal ward for:**

    5.1. *Monitoring*:

    - Routine observations (with 6 hourly temperature, pulse and respiratory rate) and
      daily CTGs if vaible

    - Monitor for signs of chorioamnionitis

    - Daily pad checks

    - Daily kick charts

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5.2. *Management:*

- Antenatal corticosteroid administration ⎫ Sure gestation of 26w0d – 33w6d
- Routine empiric antibiotic therapy for 7 days ⎭ Unsure gestation EFW 800g – 1850g
- Therapeutic tocolysis if PTL and <48hrs after 1st steroid administration and with no contraindication for tocolysis.

6. Adequate patient counselling should be given:

6.1. She must not sit in bath, but should use shower

6.2. Patient allowed to go herself to toilet and mobilize

6.3. Encouraged to monitor fetal movement (with kick chart)

6.4. To notify medical personnel if

- Any contractions felt
- Fevers or chills
- Foul discharge on pad
- Any vaginal bleeding

7. Nursing instructions on prescription chart:

7.1. Needs 6hourly temperature and vitals monitoring. (BP, P, RR)

7.2. Twice daily pad checks

7.3. Daily CTG

7.4. To notify the doctor on duty if any of the following-

- Vaginal bleeding
- Foul / purulent discharge on pad
- Maternal fever (>37.8°C), tachycardia (>100bpm)
- Any abnormality on CTG

8. If no more amniotic fluid drainage for > 24h and > 48h after 1st steroid administration:

8.1. Keep as inpatient till 34w0d and then arrange for delivery

8.2. Stop antibiotics after the full 7day course (and only if no clinical signs of infection)

8.3. Risk for chorioamnionits and infection still continuous although there is no more documented drainage, if out patient management is considered then involve your consultant with this decision and advise your patient about all the risks involved. Make clear notes of this decision in the file.

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F.   MANAGEMENT: GESTATIONAL SPECIFIC / DEFINED:

1.   PPROM IN ≥ 34W0D SURE GESTATION:

  [if Unsure an EFW ≥ 1850g]

  1.1. Expeditious delivery

  1.2. Broad spectrum antibiotics if suspected chorioamnionitis or > 24h ROM

  1.3. If the patient is stable and low risk then she can be induced with oral misoprostol in the antenatal ward.

  NOTE - *These patients can be referred for the PPROMPT study – Sr van Papendorp / Prof Hall*

2.   MANAGEMENT: PPROM IN 26W0D – 33W6D SURE GESTATION

  [If Unsure an EFW 800g - 1850g]

  2.1. Admit to antenatal ward for conservative management if rupture confirmed; and there are no signs of clinical chorioamnionitis, no fetal distress or other contra-indications for further conservative management

  2.2. Administer corticosteroids and antibiotics.

  2.3. Routine prophylactic tocolysis is not needed.

  2.4. If contractions develop in the first 24 hours of conservative management, therapeutic tocolysis can be added to allow the corticosteroid duration to reach 48 hours.

  2.5. Deliver if amnionitis, abruption, advanced labour, suspicious or pathological CTG or sure gestation of ≥ 34w0d.

3.   PPROM IN 24W0D – 25W6D SURE GESTATION:

  [If Unsure an EFW 550g - 800g]

  3.1. If there are no risk factors, the patient can be evaluated for conservative management. These patients should first be discussed with your consultant

  3.2. Routine care as for Conservative Management of PPROM can be followed with the following exceptions:

  • Routine steroids should not be administered at the time of ROM at these gestations but should be given when > 26w0d sure gestation or EFW > 800g if unsure gestation is reached.

  3.3. No indication for routine tocolysis - If PTL at these gestations then best not to suppress labour.

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4. **PPROM IN < 24W0D SURE GESTATION:**

[If Unsure an EFW < 550g]

4.1. If the gestational age is 24 weeks or less, the fetal prognosis is poor and adequate counseling must be done (by a consultant or registrar) on the continuation of the pregnancy.

4.2. Induction of labour / termination of pregnancy is advised

4.3. If patient insists on conservative management then:

- Exclude amnionitis, abruption, fetal abnormality and contraindications for conservative management.
- Ensure maternal condition is stabilized
- Screen for high chorioamnionits risk

4.4. Then evaluate for conservative management after discussion with your consultant for:

- In patient management
- Routine empiric antibiotics for 7 days
- Routine steroids should not be administered at these gestations (To be given when sure gestation > 26w0d or EFW > 800g if unsure gestation is reached)

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G. MANAGEMENT: ROLE OF TOCOLYSIS IN PPROM:

1. **Value**

   1.1. There is no place for prophylactic tocolysis in PPROM

   1.2. Tocolytic therapy has been shown to prolong pregnancy to provide benefit of administering antenatal corticosteroids if patient is in PTL.

   1.3. Tocolytic therapy may play a role in safe transport for women with preterm labour.

2. **Indication for Tocolysis in PPROM**

   2.1. Women in *preterm labour* 26w0d-33w6d sure gestation or EFW 800g – 1850g if gestation is unsure

3. **Contraindications for Tocolysis**

   3.1. Mother does not consent to suppression

   3.2. If ≥ 34w0d sure gestation or EFW ≥ 1850g in unsure gestation

   3.3. Pathological or suspicious fetal heart rate pattern

   [CTG monitoring in sure gestation > 27w0d or Unsure gestation EFW > 800g]

   3.4. Lethal fetal anomaly

   3.5. Intra uterine fetal death

   3.6. Suspected chorioamnionitis (clinical signs of infection)

   3.7. Severe hypertensive conditions in pregnancy

   3.8. Abruptio Placentae

   3.9. Severe IUGR (<3rd percentile)

4. **Relative contraindications for Tocolysis**

   4.1. If less than 26w0d sure gestation or EFW < 800g if the gestation is unsure

   4.2. Antepartum haemorrhage of unknown cause

   4.3. HIV positive patients / Immunocompromised patients

5. **Drugs & Dose**

   5.1. Calcium channel blocker: Short acting Nifedipine (Adalat®)

   To be used as 1st line treatment

   - Dose: 30 mg loading dose orally (do not chew or take sublingually) and 20 mg 3 hours later. If still contractions, continue with 20 mg 6 hourly per os for 48 hours.
   - Contraindications: All cardiac diseases, hypotension and hypertension diseases. (Unless discussed and decision made by consultant – make clear notes!)
   - Side effects: Flushing, headache, dizziness, nausea

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5.2. Prostaglandin synthetase inhibitor – Indomethacin (Indocid®)

To be used as 2ⁿᵈ line treatment after Nifedipine, if initial tocolysis was not successful.

- Dose: 100mg rectal suppository 12hly for 3 doses
- Contraindications: pre-existing gastrointestinal ulcers/lesions, known allergy to NSAIDS, significant renal or hepatic impairment, sure gestation of ≥ 32w0d (If unsure gestation an EFW ≥ 1500g)
- Side effects: Nausea, heartburn, fluid retention, and suppression of platelet function.
- **NOTE:** *Concomitant use of Nifedipine and Indomethacin as initial management for tocolysis should only be prescribe under consultant guidance*

→If at this stage tocolysis is not effective in stopping the contractions, the use of a beta₂ stimulant (Salbutamol) as an adjunct in the dosage can be considered.

5.3. Beta-mimetic – Salbutamol (Ventolin®)

- Dose: 250 μg (0.5ml of 500μg ampoule diluted in 20ml saline) slowly IV as soon as possible

  Can continue infusion: 2mg (4 ampoules) in 200ml saline at 1ml/minute and increase every 10 minutes by 1 ml/minute until maximum of 4ml/minute or pulse >120 bpm.
- Contraindication Cardiac arrhythmias, maternal tachycardia (pulse > 110bpm), all underlying cardiac and diabetic disease. (Unless discussed and decision made by consultant – make clear notes!)
- Side effects Cardiac or cardiopulmonary arrhythmias, pulmonary oedema, myocardial ischemia, tachycardia, hypotension

NB! *Salbutamol infusions can only be started if the maternal monitoring can be done with continuous ECG and oxygen saturation monitoring. Increase salbutamol dosage until contractions is suppressed **OR** pulse rate 110-120 bpm maximum.*

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H.   **MANAGEMENT: ROLE OF ANTENATAL STEROIDS IN PPROM**

1.   **Value**

1.1.   This is the most beneficial intervention for patients with PPROM

2.   **Indications**

2.1.   All pregnant women between 26w0d and 33w6d sure gestation with confirmed PPROM should receive single course corticosteroids

3.   **Relative Contraindications**

3.1.   Sever maternal infection/septicaemia

4.   **Drugs and Dose**

4.1.   Betamethsone (Celestone®)

- Dose: 12 mg IM repeat the same dosage after 24 hours

The first dose should be given as soon as possible (even at the referring centre)

> **NB!**   *The use of antenatal corticosteroids in pregnancies complicated by maternal diabetes mellitus is not contraindicated and the decision should be made with your consultant.*

5.   **Side-effects and complications:**

5.1.   May accentuate glucose intolerance/hyperglycaemia (avoid glucose screening for 48hrs and do not react on glucosuria)

5.2.   Pulmonary oedema (NB! Use with caution in multiple pregnancies and in conjunction with $\beta2$ stimulant use)

6.   **Repeated Dosages**

6.1.   Repeat courses of antenatal corticosteroids should be given only according to consultant opinion.

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I. **MANAGEMENT: ROLE OF ANTIBIOTICS IN PPROM:**

1. **Value**

    1.1. Antimicrobial cover in women with PPROM is given to treat or prevent ascending decidual infection.

2. **Indication for antibiotics**

    2.1. Overt maternal or fetal infection.

    2.2. Women with preterm labour with ruptured membranes.

    2.3. Women with preterm rupture of membranes without labour.

3. **Drugs & Dose**

    3.1. No clear first line drug but the following drug can be used

    - Ampicillin 2g every 6 hours for 48 hours, then oral amoxicillin 500g 8 hourly for 5 days

        combined with

    - Azithromycin 1g orally single dose

    - **Add** Metronidazole 400mg 8 hourly orally for 5 days **if** there are clear signs of symptomatic bacterial vaginosis on wet mount smear.

Ⓘ **NB! Antimicrobial recommendations:**

These recommendations are based upon expert opinion and data extrapolated from NICH, Oracle I and Cochrane 2006 review including data from current recommendations from O&G Colleges around the world.

This is a cost effective and easy administrable management option for our population and this is therefore the recommended treatment for Tygerberg Hospital.

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**J.** **MANAGEMENT: DISCHARGE ADVICE AFTER PRETERM BIRTH**

1. Ensure that the discharge note is in the possession of the patient with adequate advice for the next pregnancy. Advise the patient on the importance of a pre-conceptual visit and advice.

2. Patients with preterm birth and poor outcome need to be followed at the postnatal clinic in 6 weeks for placenta histology / baby autopsy results and / or infectious / chromosomal screening.

3. Identify selected patients at discharge [After telephonic counselling with Special Care/Maternal Medicine] who should book at Special Care clinic for preconceptional counselling and screening when the next pregnancy is planned again.

4. If pregnant, book at nearest local clinic and ask for referral to a high-risk antenatal service. (Bring along current discharge note if possible.)

AUTHORISED BY	GS Gebhardt
COMMITTEE RESPONSIBLE	GS Gebhardt, L Geerts, DR Hall, JL van der Merwe, E Decloedt
DATE REVISED	
DATE EFFECTIVE	1 July 2012
REVIEW DATE	31 December 2016
EVIDENCE	Evidence basis for the above decision is available on request

Signed: GS Gebhardt

Head: general specialist services; Obstetrics and Gynaecology

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Summary for Management of Preterm Prelabour Rupture of Membranes (PPROM)

Suggestive early symptoms:
- Low abdominal pain/cramps/pressure
- Low backache
- Increased vaginal discharge
- Bleeding/spotting/show

General Assessment

Risk Assessment

Management of Cord Prolapse ← Cord prolapse — **Urinalysis Urine Culture Speculum Examination Wetmount** → Imminent delivery — • Notify Paeds • Prepare for delivery

Admission + Observations [If pad wet – repeat speculum] ← No, but highly suspicious — **Confirmed PPROM**

Any Signs of Chorioamnionitis / Contraindication for Conservative Mx

| Sure gestation < 24w0d Unsure gestation | Sure gestation 24w0d - 25w6d Unsure gestation | Sure Gestation 26w0d - 33w6d Unsure gestation | Sure gestation > 34w0d or more Unsure gestation EFW > 1850g |

- Section F Sub-Section 4
- Section F Sub-Section 3
- Section F Sub-Section 2
- Proceed to delivery

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Appendix II. 23-item tool to measure protocol fidelity

Items related to initial admission		Yes	No	Not indicated
1	Was a clear history documented?			
2	Was gestation calculated correctly?			
3	Were maternal vital signs documented?			
4	Was urine disptix documented?			
5	Was hydration status documented?			
6	Was uterine activity documented?			
7	Was ultrasound performed at admission?			
8	Was baseline CTG documented? (Not indicated if fetus not viable yet)			
9	Was a sterile speculum performed?			
10	Was a visual assessment of the cervix documented?			
11	Was a ward Hb done?			
12	Was a new MSU sent for culture and sensitivity?			
13	Were clear nursing prescriptions given regarding routine observations as per protocol?			
14	Were there any contra-indications for conservative management?			
15	Was antibiotics prescribed as per protocol?			
16	Was adequate patient counselling documented?			
Items related to in-patient stay		Yes	No	Not indicated
17	Was patient checked twice a day for signs of chorioamnionitis?			
18	Was a daily kick chart done?			
19	Were pad checks done daily?			
20	Was BMZ given correctly?			
21	Was antibiotics administered correctly?			
22	Was tocolysis given when prescribed? (Only indicated with contractions within the first 48 hours after admission)			
23	Was results of special investigations documented?			