Elective delivery of women with a previous unexplained intra-uterine fetal death at term (≥ 39 weeks): A prospective cohort study at Tygerberg Hospital, South Africa.

Dissertation presented in partial fulfilment for the Degree of Master of Medicine in the Faculty of Medicine and Health Sciences, at Stellenbosch University.

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A prospective cohort study at Tygerberg Hospital, South Africa
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.

Signature

Date: 25 March 2014
Abstract

Introduction

Pregnancies in women with a previous unexplained stillbirth may be jeopardized by increased antenatal surveillance and higher rates of induction of labour and caesarean delivery without clear evidence of benefit. Despite the fact that there have been no studies that adequately tested fetal benefit in routine induction of labour for a previous stillbirth, a policy of routine induction of labour at 38 weeks, with all the associated maternal, fetal and health-care associated costs, was in practice at Tygerberg Hospital for the past 30 years. This study aimed to investigate the safety of continuation of these pregnancies until term (≥39 weeks).

Aims and Objectives

To assess the clinical outcome and impact on the health service in a pregnancy with a previous unexplained intra-uterine demise (IUD) by routine induction of labour at term instead of at 38 weeks.

Methodology

This was a prospective observational study on the safety of a new hospital protocol which was introduced in 2012. The protocol extended the gestation for induction after a previous IUD from 38 weeks to term. The study population included all pregnant patients with a current singleton pregnancy, and a previous unexplained or unexplored (no data available) singleton fetal demise ≥24 weeks/500grams. All patients with a previous stillbirth in the metropolitan drainage area of Tygerberg Hospital are referred to Tygerberg for further care; and all referrals during 2012 were recruited for the study. Patients with known or recurrent risks for intra-uterine death...
were managed according to the relevant clinical condition and were excluded from the study.

Results

During the audit period, 306 patients with a previous intra-uterine fetal death were referred for further management. Of these, 161 had a clear indication for either earlier intervention or no intervention and were excluded from the protocol. Of the remaining 145 patients, 9 met exclusion criteria and there were 2 patients who defaulted. Forty-two of the study patients (with no known previous medical problems) developed complications during their antenatal course that necessitated a change in clinical management and earlier (<39 weeks) delivery. Of the remaining 92 patients in the audit, 47 (51%) went into spontaneous labour before their induction date. There were no intra-uterine deaths prior to delivery.

Conclusions

Careful follow up at a high risk clinic identifies new or concealed maternal or fetal complications in 29% of patients with a previous IUD and no obvious maternal or fetal disease in the index pregnancy. When all risks are excluded and the pregnancy allowed to progress to 39 weeks before an induction is offered, 51% will go into spontaneous labour.
Opsomming

Inleiding

Swangerskappe in vroue met vorige onverklaarbare stilgeboorte mag in gevaar gestel word deur meer intense voorgeboorte sorg en ‘n groter hoeveelheid induksies van kraam en keisersnitte sonder duidelike bewyse dat dit tot voordeel strek. Ten spyte van die feit dat daar geen studies is wat bewys het dat roetine induksie van kraam vir ‘n vorige stilgeboorte op 38 weke tot voordeel van die baba was nie, was ‘n beleid van roetine induksie van kraam op 38 weke, met al die geassosieëerde moederlike en fetale risikos daaraan verbonde; asook die hoë gesondheidskostes, roetine praktik in Tygerberg Hospitaal vir die afgelope 30 jaar. Hierdie studie het ten doel gehad om die veiligheid van voortsetting van hierdie swangerskappe tot voltyd (≥39 weke) te ondersoek.

Doelwitte

Om die kliniese uitkoms; asook die impak op gesondheidsdienste te evalueer in ‘n swanger vrou met ‘n vorige onverklaarbare intra-uteriene sterfte; deur roetine induksie van kraam aan te bied op voltyd in plaas van 38 weke.

Metodologie

Hierdie was n prospektiewe kohort studie om die veiligheid van ‘n nuwe hospitaal protokol wat in 2012 geïmplimenteer is, te bepaal. Hierdie protokol het die gestasie tydperk van induksie van kraam van alle swanger pasiënte na ‘n vorige onverklaarbare stilgeboorte van 38 weke na voltyd verleng. Die studiepopulasie het alle swanger pasiënte met ‘n huidige enkelswangerskap en ‘n vorige onverklaarbare of onbekende (geen data beskikbaar) enkelvoudige fetale sterfte ≥24 weke/500gram,
ingesluit. Alle pasiënte in die metropolitaanse dreineringsarea van Tygerberg Hospitaal met 'n vorige stilgeboorte word na Tygerberg verwys vir verdere hantering, en alle verwysings gedurende 2012 was gewerf vir die studie. Pasiënte met bekende of herhalende risikofaktore vir 'n intra-uteriene sterfte was hanteer volgens die relevante kliniese inligting en was uitgesluit by die studie.

Resultate

Drie-honderd-en-ses pasiënte met 'n vorige intra-uteriene fetale sterfte was gedurende die oudit periode verwys vir verdere hantering. In 161 pasiënte was daar 'n duidelike indikasie vir of vroeër intervensie of geen intervensie nie; en hulle was uitgesluit van die protokol. Van die oorblywende 145 pasiënte is 9 pasiënte uitgesluit as gevolg van die uitsluitingskriteria en daar was 2 pasiënte wat versuim het om op te volg. Twee-en-veertig pasiënte (met geen bekende vorige mediese probleme nie) het komplikasies gedurende hulle voorgeboorte verloop ontwikkeld wat gelei het tot verandering in kliniese hantering en vroeëre verlossing (≤39 weke) genoodsaak het. Van die oorblywende 92 pasiënte in die oudit, het 47 (51%) in spontane kraam gegaan voor hulle induksiedatum. Daar was geen intra-uteriene sterftes voor verlossing nie.

Gevolgtrekkings

Noukeurige opvolg by 'n hoërisiko kliniek identifiseer nuwe of versteekte moederlike en fetale komplikasies in 29% van pasiënte met 'n vorige intra-uteriene sterfte sonder enige duidelike moederlike of fetale siekte in die indeks swangerskap. Wanneer alle risikos uitgesluit word en die swangerskap toegelaat word om voort te gaan tot 39 weke voor 'n induksie aangebied word, sal 51% van pasiënte spontaan in kraam gaan.
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Contents

Declaration ........................................................................................................................................... ii

Abstract .............................................................................................................................................. iii

Opsomming ........................................................................................................................................ v

Acknowledgements ............................................................................................................................... vii

Contents ............................................................................................................................................... viii

List of Tables ....................................................................................................................................... xi

List of Figures ...................................................................................................................................... xii

List of Abbreviations ............................................................................................................................ xiii

Glossary ................................................................................................................................................. xiv

1. Introduction ........................................................................................................................................ 1

1.1 Background ................................................................................................................................... 1

1.2 Problem Statement ......................................................................................................................... 1

2. Literature Review ............................................................................................................................. 3

2.1 Introduction .................................................................................................................................. 3

2.2 Literature review ........................................................................................................................... 4

2.2.1 Determinants of unexplained intra-uterine fetal death......................................................... 5

2.2.2 Recurrence risks for IUD ......................................................................................................... 7

2.2.3 Antenatal surveillance ............................................................................................................. 13

2.2.4 Consensus statements and best practice ................................................................................. 14

2.2.5 The potential risk of late onset intra-uterine growth restriction .............................................. 15

2.2.6 The potential morbidity associated with early term delivery ................................................ 15
2.3 Summary ..................................................................................................... 16

3. Study design ...................................................................................................... 17

3.1 Setting ......................................................................................................... 17

3.2 Participants .................................................................................................. 18

3.3 Exclusion criteria ......................................................................................... 18

3.4 Data collection ............................................................................................. 18

3.5 Variables ..................................................................................................... 19

3.6 Study size .................................................................................................... 19

3.7 Statistical methods ...................................................................................... 20

3.8 Ethics ........................................................................................................... 20

4. Findings and Analysis ........................................................................................ 21

4.1 Participants .................................................................................................. 21

4.2 Descriptive data ........................................................................................... 26

4.3 Follow-up of patients during antenatal care ................................................. 28

4.4 Outcome: Maternal ..................................................................................... 29

4.4.1 Spontaneous labour vs induction of labour rate ...................................... 29

4.4.2 NVD vs Caesarean section rate ............................................................ 32

4.4.3 Admission-to-Hospital – Start-of-Induction Time ................................... 33

4.4.4 Start-of-induction – Delivery time .......................................................... 33

4.4.5 Delivery-to-discharge time: Normal vertex delivery and caesarean section respectively ................................................................. 34

4.4.6 Admission-to-Discharge time: Comparison between spontaneous labour vs. induction of labour for patients with normal vertex deliveries ............. 35
4.5 Outcome: Fetal

5. Conclusion

5.1 Summary of Findings

5.2 Limitations

5.3 Interpretation and conclusion

5.4 Future research

6. Funding

Appendix A: Protocol for management of a patient with a previous unexplained/unexplored IUD

Appendix B: Ethics committee approval

References
List of Tables

Table 1: Etiology of previous stillbirths as determined from history and/or clinical notes or available histology ................................................................. 22

Table 2: Exclusion criteria from audit ................................................................ 23

Table 3: Complications that necessitated earlier delivery in patients with previous intra-uterine fetal deaths ................................................................. 24

Table 4: Characteristics of the study group ....................................................... 26

Table 5: Booking blood characteristics of patients at booking ............................ 27

Table 6: Breakdown of gestational age at delivery ............................................. 30

Table 7: Reason and duration for admissions of newborns .............................. 36
List of Figures

Figure 1: Flow diagram of study patients ................................................................. 25
Figure 2: Health status of patients at booking .......................................................... 27
Figure 3: Social habits of patients at booking .......................................................... 28
Figure 4: Gestation calculation ................................................................................ 31
Figure 5: Caesarean section rate and reasons for Caesarean section in each group ......................................................................................................................... 32
Figure 6: Respective timeframes from induction of labour to delivery ..................... 34
List of Abbreviations

BMI: Body mass Index
CS: Caesarian section
EDD: Estimated date of delivery
HAART: Highly active antiretroviral therapy
HIV: Human immunodeficiency virus
IUD: Intra-uterine demise
IUFD: Intra-uterine fetal demise
ICU: Intensive care unit
IOL: Induction of labour
IUGR: Intra-uterine growth restriction
LNMP: Last normal menstrual period
NVD: Normal vertex delivery
OR: Odd Ratio
PPIP: Perinatal Problem Identification Program
RI: Resistance index
RR: Relative risk
RVD: Retroviral disease
Glossary

Fetal death (stillbirth): The World Health Organization defines stillbirth as a ‘fetal death late in pregnancy’ and allows each country to define the gestational age at which a fetal death is considered a stillbirth for reporting purposes. As a result, some countries define stillbirth as early as 16 weeks of gestation, whereas others use a threshold as late as 28 weeks. Fetal deaths under the threshold are considered products of miscarriage in South-Africa and for the purpose of this study we used 24 weeks (or 500 grams birth weight if no gestation available) as the cut-off.

Unexplained stillbirth: An unexplained stillbirth is a fetal death that cannot be attributed to any known identifiable fetal, placental, maternal, or obstetrical etiology; but where appropriate work-up was done.

Unexplored stillbirth: A stillbirth where no previous notes are available and/or no attempt was made to investigate the death.

Early term(8): 37 0/7 weeks of gestation through 38 6/7 weeks of gestation.

Full term(8): 39 0/7 weeks of gestation through 40 6/7 weeks of gestation.

Late term(8): 41 0/7 weeks of gestation through 41 6/7 weeks of gestation.

Postterm(8): 42 0/7 weeks of gestation and beyond. Above distinction was made to focus attention on the increase risk for morbidity and mortality between these groups.
1. Introduction

1.1 Background

Stillbirth is one of the most common adverse pregnancy outcomes worldwide. It is difficult to manage subsequent pregnancies optimally, as there is relatively little known about pregnancy outcome after a stillbirth. It continues to be a major concern for obstetricians and neonatologists and there is much controversy around the recurrence rate and the management of a subsequent pregnancy after a previous unexplained stillbirth. There is very little evidence available to guide the optimal management in a future pregnancy. If, however, the cause of a previous stillbirth is known, it is easier to predict the recurrence risk and outcome in a subsequent pregnancy and management can be directed towards prevention of that specific cause and risk factors associated with that. Although the characteristic of pregnancies that ended in unexplained stillbirths have been studied, there is not enough information to guide obstetricians on the management of future pregnancies. Thus, subsequent pregnancies tend to be associated with increased antenatal surveillance and higher rates of induction of labour and caesarean delivery without clear evidence of benefit.

1.2 Problem Statement

At Tygerberg Hospital, for the past few decades, patients with a previous unexplained fetal demise were routinely delivered at 38 weeks of gestation. They are regarded as high risk and are appropriately referred in the four-tiered provincial maternity service to a specialist (high risk) clinic. Yet, there are no data from randomised controlled trials that directly support routine delivery at 38 weeks. In
contrast, in the past few years, several studies have confirmed that elective early pre-term delivery (before 39 weeks) jeopardizes neonatal outcome and should be avoided whenever possible. To minimise prematurity-related neonatal complications, the American College of Obstetricians and Gynecologists now recommends that elective deliveries not be performed before 39 weeks of gestation(1).

Some form of increase antenatal fetal surveillance is recommended, but does not automatically mean earlier delivery. Induction of labour before term has its own associated risks and costs. Apart from the very real danger of preterm delivery (especially when the exact gestational age is not available), increased caesarean section rate and possible complications associated with the induction agent, there are also increased costs due to longer hospital stay which is a significant additional burden on an already overcrowded health system. Based on this data, the Tygerberg and Metro-East departmental protocol to deliver women with a previous unexplained loss was changed to one of delivery at late term (at the end of 2011). The departmental protocol (Addendum 1) also aims to reduce unnecessary costs by decreasing the number of women admitted for elective delivery.
2. Literature Review

2.1 Introduction

The stillbirth rate for babies ≥500g is still unacceptably high in South Africa at 42.87/1000 in the general population (for all levels of care)(2). In the relatively homogenous population served by a large referral institution (Tygerberg Hospital) in the Western Cape it was 24.5/1000 in 2011; a gradual but substantial decrease from 32.1/1000 over the last 40 years(3). In otherwise low-risk mothers with a prior stillbirth, there can be up to a 12-fold increased risk for adverse outcome in the subsequent pregnancy(4). The biggest risk (with a hazard ratio of 10.3, 95% CI 6.1–17.2) for repeat stillbirth is before 28 weeks. In a large population based study, the adjusted odds ratio for subsequent death was 7.1 (95% CI 3.2–15.7)(5). The risk for adverse outcome extends into the first year of life - the infant mortality rate of women with a prior stillbirth was 2.5 times higher (AHR=2.51, 95% CI: 1.73–3.65) in a large, retrospective population-based study(6).

When the cause for the stillbirth is known, it is easier to devise a plan for future pregnancies. However, there is very little evidence available to guide the optimal management of a future pregnancy after a stillbirth of unknown cause, and no studies have confirmed a fetal advantage for routine induction of labour in subsequent pregnancies(7). Elective delivery before term seemed like a logical option, and in many centres elective early term (as per the American College of Obstetricians and Gynecologists (ACOG) definition of 37 weeks to 38 weeks 6 days)(8) delivery was offered to women with a prior stillbirth for unknown cause. The stillbirth rate declined slightly in the US (from 7.5 to 6.2 per 1000) from 1990 to 2003 at the same time as
the rate of elective delivery before term increased; but that reduction occurred at 40 weeks or more(9). There was no corresponding reduction in the stillbirth rate for the preterm or early term period. As there is no current evidence to suggest that late preterm inductions will reduce the stillbirth rate, the ACOG do not currently recommend iatrogenic delivery before 39 completed weeks except for specific maternal or fetal conditions (10).

With the use of a rigorous classification system and software (the Perinatal Problem Identification Program)(11) as well as institutional review of every death with post-mortem and/or placental histology where applicable, only 8.8% of stillbirths at Tygerberg are classified as of “undetermined/unknown” cause(12). The routine management in subsequent pregnancies at Tygerberg Hospital for the past 30 years included induction of labour at 38 weeks of gestation. Based on a thorough review of the literature, to follow below, as well as international opinion which suggested that the ideal timing of delivery in most pregnancies after a prior stillbirth is at 39 weeks’ gestation(13), the routine induction of labour policy for a prior stillbirth of unknown cause at Tygerberg was changed from 38 weeks to term (≥39 completed weeks). The current study is an audit of the outcome the first year after implementation.

2.2 Literature review

A literature search of all published English language articles dealing with subsequent pregnancy outcome after a previous unexplained intra-uterine death were conducted using PubMed®(14) with keywords that included “unexplained stillbirth”, “delivery prior stillbirth” and “management stillbirth”. The references from all articles identified were scrutinised to find similar articles.
It is important to note that most of the published literature on stillbirths deals with the complete issue (e.g. it includes stillbirths due to known causes, congenital abnormalities, deaths due to maternal disease or known risk factors for recurrence) and not with unexplained deaths only. Over the years, improvements and refinement in ultrasonography and placental histopathology have contributed to finding the cause for an intra-uterine death; yet in up to 25% of cases the deaths remains unexplained. The important question is what the recurrent risk of an unexplained stillbirth is on the risk of future recurrence at term. Many of the older studies on unexplained stillbirths may in fact have included deaths where more modern techniques would have identified a cause of death. In these studies it is important to distinguish unexplained (no cause found after thorough investigations) from unexplored (death not thoroughly investigated) cases.

A good definition of unexplained intra-uterine fetal death is given by Froen(15) as death “before the onset of labour of a fetus at ≥22 completed weeks of gestation or with ≥500g body mass, which is unexpected by history and in which a thorough autopsy of the fetus, together with gross and histologic examination of the umbilical cord, placenta, and membranes, fails to demonstrate an adequate cause of death”.

2.2.1 Determinants of unexplained intra-uterine fetal death

Heinonen and Kirkinen(16) assessed subsequent pregnancy outcome in women with a history of stillbirth as a result of causes other than maternal conditions and fetal abnormalities. In this cross-sectional study they followed all women with a prior stillbirth after 24 weeks/500grams until their next pregnancy and compared them to a group of women with no prior stillbirths. Despite an intensive work-up of the stillbirths, causes of previous stillbirths were due to unknown reasons in 29.2% of cases. Ninety-two deliveries after stillbirth were identified and compared with the general
multiparous population (n=11818 deliveries) as recorded in the birth registry at Kuopio, Finland. After controlling for obstetric risks, women with a history of stillbirth as a result of causes other than maternal conditions and fetal abnormalities were older than their unaffected controls (32.4 year vs. 30.3 year) and a stillbirth in an earlier pregnancy was associated with a significantly higher ($p < 0.001$) frequency of placental abruption in the subsequent pregnancy (5.4% vs. 0.7%). It is not mentioned in the study at what gestations these abruptions have occurred. Also, a history of stillbirth was predictive of preterm delivery ($\text{OR} = 2.25$) and low birth weight infants ($\text{OR} = 2.70$). No recurrence of fetal death was reported.

The authors concluded that a pregnancy with a history of stillbirth as a result of causes other than maternal conditions and fetal abnormalities is a moderate risk state with a good probability of a favourable outcome. However, it is important to note that in this study the women with previous stillbirth had more frequent fetal surveillance, including semi-weekly non-stress tests and amniotic fluid index assessment beginning two weeks before the gestational age of the previous stillbirth. If the above results were non-reassuring, a contraction stress test or a biophysical profile was carried out and induction of labour or caesarean delivery was performed if these tests were non-reassuring. The authors lastly concluded that if the cause of previous fetal death remains undetermined, or if the fetal death follows an obstetric complication such as cord accident or placental abruption that can recur but cannot be predicted, it was unlikely that there would be benefit from increased antepartum fetal monitoring. They suggest that a history of stillbirth should be an indication for increased fetal surveillance rather than earlier elective delivery and that most pregnancies may be safely delivered at term.
Frøen and co-workers(15) reported; based on data extracted from the Medical Birth Register of Norway for all Oslo deliveries between 1986 and 1996, that 25% of the total stillbirths in that cohort (n=291) remained ‘unexplained’. The statistical significant identifiable risk factors for unexplained IUD were smoking, maternal education, obesity and glucosuria (but not a prior stillbirth); all of which can be identified with basic antenatal care. Regrettably, many cases of possible gestational diabetes were not further explored or investigated and the authors stressed the importance of routine screening for diabetes at 24-26 weeks; this recommendation also became part of the Tygerberg protocol for management of women with a previous IUD. The authors argue that ‘unexplored’ IUDs should be analysed separately as there may be concealed maternal or fetal disease that will skew the analyses.

2.2.2 Recurrence risks for IUD

Robson et al(17), using the perinatal database of South Australia, specifically identified 316 women with a prior unexplained stillbirth and matched them to 3160 multiparous women with a favourable outcome. This was a population-based retrospective cohort study from 1987–1997. Although they concluded that the study was probably underpowered, they could find no increase in the rate of stillbirth and no statistically significant increase in the rate of perinatal death (OR 1.62, 95% CI 0.63-4.20) or neonatal deaths.

There was a fourfold increased incidence in subsequent births of abnormal glucose tolerance or gestational diabetes. Gestational age at birth and birth weight were also significantly reduced, suggesting that birth attendants may be more motivated to undertake close fetal monitoring and to act more promptly on perceived abnormalities in fetal heart rate. In this study it is not mentioned what the different hospital policies
were on the management of a pregnancy with a previous unexplained intra-uterine death.

A rather old retrospective study (with data from the 13 preceding years) from Samueloff et al from 1993 is worth including as it serves as the reference for the often quoted 10-times increased rate of stillbirth recurrence observed after a previous stillbirth (18). There were only 34 women in this study with a recurrent stillbirth and the authors included all stillborn fetuses after 20 weeks of gestation with no attempt at distinction between causes of stillbirth.

In a similar (but even smaller) study from the Netherlands, in which they used 16 weeks gestation and above in their definition of intra-uterine death, there were 193 cases of IUD over a 5 year period of which 11 women had a second intra-uterine death (19). As it is a tertiary referral centre the number of uncomplicated deliveries in the drainage area is not mentioned. Of the 11 cases, 8 fetuses died before 24 weeks and there were two cases of repeat abruptio placentae at 29 weeks and 33 weeks respectively, and one growth restricted fetal death at 30 weeks. It was clearly a high risk, selected group of patients and in all cases there were pathology present with the first death; so it was not unexplained deaths.

Onwude and co-workers (20) did a matched case-control study using 75 women who delivered unexplained stillbirths (1992-1996) and then followed them over a period of 4 years at the St John’s Hospital in the United Kingdom. They were matched for maternal age and parity with 144 controls. The authors were confident that their study was of adequate sample size to be sufficiently powered to detect a difference; and there were no stillbirths in cases or controls at follow-up. They concluded that a woman who has had an unexplained stillbirth at term has no greater risk of recurrence than a matched control. It is important to note that the woman at risk in
this study received the usual routine antenatal care, but that their gestational age at
the next delivery was earlier (although there was not a significant difference in birth
weight).

Sharma et al(21) attempted to estimate the risk of stillbirth recurrence among
relatively low-risk women (age <35 years, singleton, non-smoking). They used the
Missouri maternally-linked cohort data set that spanned the years 1978 to 1997 in the
USA for the study. The study group was all low-risk women with a stillbirth in their
first pregnancy (n=1050), and the control group all women without. A total number of
261 384 women were included, and there were 947 cases of stillbirth in the second
pregnancy, of which 20 cases occurred in women with a prior stillbirth, giving an
adjusted 6-times higher risk for IUD. Importantly, analysis by stillbirth subtype in the
second pregnancy showed that the risk of repeat stillbirths was higher for subsequent
early (fetal deaths between 20 and 28 weeks) rather than late stillbirths (fetal deaths
at ≥ 29 weeks); and for intrapartum rather than antepartum stillbirths.

This study defined an intrauterine fetal death as any death ≥20 weeks of gestation,
which would include a large number second trimester miscarriages. As it was a
retrospective study, no information on the cause of the stillbirth (apart from those due
to congenital anomalies) was available. Their cohorts included stillbirths where
maternal conditions like diabetes and pre-eclampsia might have contributed to the
outcome. This data shows that elective induction at 38 week would not prevent any
of the early fetal deaths (which constitute the highest proportion of recurrence) and
also would not prevent intrapartum stillbirths (as these can occur at any time during
induction or spontaneous labour).

The same authors(22) then used the same cohort and time span, but with a slightly
different approach, for a further study; they identified all women (n=404 180) where
information on pregnancy outcome was available for both the first and the second pregnancy; and then identified the study group as all cases of stillbirths in the second pregnancy (n=1929). They found that a history of stillbirth was associated with a 5-fold increase risk for a subsequent stillbirth, and that this risk is almost three times higher in African-Americans as compared to whites.

A recent similar study from Turkey(23) did not add much that is not known yet; the authors compared 201 subsequent births in women with a previous stillbirth to 402 live births in women with no previous IUD. They did not find a higher rate of repeat stillbirth, but more maternal disease - the rates of pre-eclampsia, HELLP syndrome, low birth weight and malpresentation were significantly higher in the case group.

Black et al(24) showed that the risk of a second stillbirth is not increased in the absence of known risk factors. They compared obstetric outcomes in the pregnancy subsequent to intrauterine death with that following live birth in the first pregnancy. It was a retrospective cohort study of all women who had their first and second deliveries in the Grampian region of Scotland (1976 to 2006). Women delivering for the first time between 1976 and 2002 were followed until 2006 to study their subsequent pregnancy; again using those with an IUD in their first pregnancy as the study cohort.

The main outcome measures were maternal and neonatal outcomes in the second pregnancy. Women with a prior IUD had an increased risk of pre-eclampsia (OR 3.1, 95% CI 1.7-5.7); placental abruption (OR 9.4, 95% CI 4.5-19.7); induction of labour (OR 3.2, 95% CI 2.4-4.2); instrumental delivery (OR 2.0, 95% CI 1.4-3.0); elective (OR 3.1, 95% CI 2-4.8) and emergency caesarean deliveries (OR 2.1, 95% CI 1.5-3.0); and prematurity (OR 2.8, 95% CI 1.9-4.2); low birth weight (OR 2.8, 95% CI
1.7-4.5) and malpresentation (OR 2.8, 95% CI 2.0-3.9) of the infant as compared with the control group.

The adjusted odds ratio for recurrent stillbirth was not significant (1.2 and 95% CI 0.4-3.4). They concluded that the majority of women with a previous stillbirth have a live birth in the subsequent pregnancy, but that they remain a high-risk group with an increased incidence of adverse outcomes. A subset of women; those with a previous unexplained intrauterine death (44% of all stillbirths) were of particular interest. When adjusted for pre-eclampsia, abruption, preterm delivery and low birth weight there was not a significant higher incidence of recurrent loss. This adds strength to the other studies already discussed that indicate an overall increased risk of recurrence of stillbirth, but not necessarily when the previous stillbirth is unexplained.

As this study did not reach significance in the total risk of recurrence, Bhattacharya et al(25) extended the sample size nine-fold by including data from the Scottish Morbidity Records on first deliveries beyond 24 weeks of gestation (1981 to 2000). This study increased the population size to 2677 and 306 627 women in the stillbirth and live birth groups respectively. They could now conclude that the odds of recurrence of stillbirth in the second pregnancy was 1.94 (99% CI 1.29-2.92) after adjustment for potential confounders (pre-eclampsia, abruption, preterm delivery and low birth weight). They could not repeat the analysis for unexplained stillbirths, as information on the cause of stillbirth was not available and therefore all women with a stillbirth in the first pregnancy were included. During the 20 year span of this study there were many advances made in antenatal care that could have influenced the outcomes.

Numerous factors could potentially explain the discrepancy in the findings between the original study and this study, particularly the finding that the recurrence risk of
stillbirth is increased even after adjusting for confounding factors. The authors could not adjust for maternal body mass index (BMI) (which was not available in the current dataset) and other possible confounding factors (e.g. marital status and smoking, which was also not available). Also, the demography of the women in the Grampian region were different from the entire Scottish population and the authors acknowledge that it would have been ideal to remove them from the current study, but because of data collection procedures it was not possible to identify women who were present in both datasets.

Frias et al(26) took the definition of fetal death right back to the first trimester - women (n=230) referred for evaluation of recurrent fetal death (occurring at ≥10 weeks of gestation) and having at least one subsequent pregnancy. Patients with antiphospholipid antibodies were excluded. These 230 women had a total of 721 pregnancies, resulting in 268 (37%) live births, 230 (32%) fetal deaths, and 200 (28%) spontaneous abortions. After recruitment, these women had 839 subsequent pregnancies, resulting in 202 (24%) live births, 209 (25%) fetal deaths, and 372 (44%) spontaneous abortions. According to these findings, women with a prior fetal death (after 10 weeks) are at high risk for subsequent pregnancy loss and recurrent fetal death, with fewer than 25% of pregnancies resulting in surviving infants.

However, this study looked primarily at patients with second-and third-trimester pregnancy loss and the 230 patients that met the inclusion criteria already constituted a high risk group as they had a total of 721 pregnancies of which 28% was lost before 10 weeks, and 32% lost after 10 weeks. Most of the first fetal deaths (76%) occurred in the second trimester and the majority of subsequent fetal demises were also in the second trimester (mostly 16-18 weeks).
There were no subsequent fetal demises between 37 and 39 weeks of gestation, only a small proportion between 34 and 36 weeks and again after 40 weeks. Thus, induction of labour at 38 weeks would not have prevented the losses between 34 and 36 weeks and induction at 40 weeks would potentially only prevent the losses after 40 weeks. Less than 3% of women in the study underwent a comprehensive evaluation to find a reason for the first loss, and over half had no investigation into possible reasons of recurrent fetal death.

2.2.3 Antenatal surveillance

A history of prior stillbirth is usually accepted as an indication for antepartum fetal heart rate testing, although this issue remains controversial. Weeks et al(27) tried to answer this question with a non-concurrent cohort study of patients who were seen for antepartum surveillance from January 1979 to December 1991 with a history of stillbirth as the only indication for testing. The database covered a 12-year period, involving 70 000 tests on 15 000 patients. Fetal testing in the subsequent pregnancy was analysed and only one case of recurrent stillbirth occurred among the 300 study patients. Nineteen patients (6.4%) had one or more positive antepartum surveillance tests (positive contraction stress test or biophysical profile ≤ 4). Three patients were delivered for positive tests at < 36 weeks, one by caesarean section for fetal distress. Although there was no relationship between the gestational age of the previous stillborn and the incidence of abnormal tests of fetal distress in subsequent pregnancies, they still recommend that antepartum surveillance should begin at ≥ 32 weeks in healthy pregnant woman with a history of stillbirth, as earlier testing may only increase patient and physician anxiety.
2.2.4  Consensus statements and best practice

Both the Royal College and the American College of Obstetricians and Gynaecologists have issued guidelines dealing with late intra-uterine deaths (7)(1). Due to the lack of robust information, the Royal College of Obstetricians and Gynaecologists’ guideline no. 55 can only make Best Practice recommendations on the care in future pregnancies in women who have had a late intra-uterine fetal death after 24 completed weeks of pregnancy with a singleton fetus. They emphasise that there have been no studies that have tested fetal benefit from routine induction of labour. The guideline recommends routine obstetric antenatal care and screening for gestational diabetes and that maternal request for scheduled birth should take into account the gestational age of the previous IUFD, previous intrapartum history and the safety of induction of labour. No further guidelines are given in terms of the exact timing and method of delivery. The guidelines also further recommends that a previous unexplained IUFD is an indication for birth at a specialist maternity unit.

The ACOG practice bulletin no. 22 estimate the risk of recurrent stillbirth (after 20 weeks) in low-risk women with unexplained stillbirth, at 7.8-10.5/1000 with most of this risk occurring before 37 weeks of gestation. The risk of recurrent stillbirth after 37 weeks is very low at 1.8/1000. The evidence on which this is based is not referenced. The guideline further emphasizes the fact that there is little evidence-based data to guide the treating clinician in the antepartum surveillance of a patient who had a previous unexplained stillbirth. They suggest that women with a history of stillbirth should have antepartum testing from 32-34 weeks of gestation, keeping in mind that this approach may be associated with potential morbidity and cost. The guidelines also further mention that the decision to proceed with early delivery to
prevent stillbirth must incorporate an understanding of the increased risks of maternal and neonatal complications compared with the potential benefits.

2.2.5 The potential risk of late onset intra-uterine growth restriction

There are many different classification systems for IUDs and many of them try to minimise the number of cases in the ‘unknown’ category by attributing these deaths to intra-uterine growth restriction, especially later onset IUGR that may not be easily detected with routine antenatal care. By allowing women with a previous unexplained IUD (that may have been due to undetected IUGR) to proceed to term before offering elective delivery may theoretically exposed them to a risk of recurrent IUGR and fetal death before term. The perinatal mortality database from Tygerberg Hospital for 2002-2013 (12 full years) includes 3473 stillbirths of which 294 deaths (8.47%) were attributed to idiopathic intra-uterine growth restriction (out of 72 968 total deliveries- 0.40% of all deliveries)(12).

Of these, 90 had patient-related preventable factors (never booked or did not respond to decreased fetal movements); of the remaining 204/3473 (5.87%) with IUGR, 144 were ‘early’ onset IUGR (before 30 weeks; weight <1500g). This leaves 60 babies (in 12 years; 0.8/1000 of deliveries) who died due to IUGR after 30 weeks (that is about 5 babies per year in this hospital). The data did not include maternal condition at birth.

2.2.6 The potential morbidity associated with early term delivery

In recent years much emphasis was placed on the morbidity involved in delivery before 39 weeks of gestation. Babies born during late preterm (34 weeks to 36 weeks 6 days) and early term (37 weeks to 38 weeks 6 days) are at higher risk for morbidities and mortality during and after the birth than infants born after 39
weeks (28)(29). This morbidity is not only restricted to the neonatal stage - a large population-based study by Mackay (30) used school census data and linked birth data to special education needs for children between 4 and 19 years. There was an increased rate of infants born at 37–39 weeks that required special needs - early term infants accounted for 39.6% of special education services at school age.

To achieve a balance between the hazards of too early delivery and the danger of stillbirth if a pregnancy continues past a certain gestation continue to pose a specific challenge (31).

### 2.3 Summary

From the literature review, the following deductions can be made:

- A history of a prior stillbirth (all causes) has a risk for repeat stillbirth that could be as high as 10 times.
- The risk for recurrence is greatest between 20 and 28 weeks.
- There is a higher incidence of maternal disease in the second pregnancy, especially hypertension and diabetes.
- The risk for recurrence of IUD after a previous unexplained IUD does not seem to be higher than the general population background risk.
- There is no evidence to support earlier delivery in women with a prior IUD of unknown cause.
- The risk of late-onset IUGR (in the Tygerberg population) is low (0.8/1000).
3. Study design

This study is a prospective cohort study conducted at Tygerberg Hospital, South Africa. Patients with a previous intra-uterine fetal demise that were included in the study were followed up according to an existing hospital protocol (addendum 1) and induction of labour was offered at term (≥39 weeks). The protocol was changed as part of routine hospital policy and did not form part of this study - the present study was only an audit after implementation. If the gestation of a patient was unknown, the best possible estimate was taken depending on the available data – which also used to be the practice if delivery at 38 weeks were planned. An extensive audit of the pregnancy outcome after planned routine induction of labour at term was done.

3.1 Setting

The study population included all patients with previous unexplained intra-uterine demise that were referred to Tygerberg hospital – a large metropolitan regional and tertiary referral hospital within the Western Cape province of South-Africa. Within this drainage area (estimated 2012 population size of 1 874 586) are 8 midwife-led birthing units and three large district hospitals with maternity services. According to the Western Cape Policy on level of care, these patients must be identified at primary level and referred to secondary level as soon as possible. All patients that were referred and met inclusion criteria were included in the study. Recruitment started from 1 January 2012 until 31 December 2012. Data collection was started after clients delivered and follow-up and auditing of these patients were done until the last patient delivered.
3.2 Participants

All referred pregnant patients with a singleton pregnancy and a previous unexplained or unexplored (no data available) singleton fetal demise ≥24 weeks/500 grams and; at the time of evaluation at the high risk clinic, no known maternal or fetal disease that would necessitate earlier delivery, was identified at the high risk clinic and included in the study.

3.3 Exclusion criteria

- Any maternal disease or obstetrical complication that required earlier delivery (if known at first visit to the high risk clinic) (e.g. diabetes, pre-eclampsia etc).

- Any known recurrent reason for a previous loss (auto-immune disease, uterine abnormality, anti-phospholipid syndrome, fetal thrombotic vasculopathy, parental chromosomal translocation carrier, metabolic diseases, documented abruptio placentae etc.).

- Any non-recurrent reason for the previous loss (syphilis, cord prolapse, birth asphyxia, trauma etc.).

3.4 Data collection

All patients that were referred and met the inclusion criteria were included in the study. Enrolment was continuous for one year (1st January 2012 until 31 December 2012).
3.5 Variables

The audit aimed to see as main outcome if it is safe to continue the pregnancy in women with a previous unknown/unexplored IUD to term and whether it does help to prevent the birth of an early term infant and decrease the number of inductions of labour. Secondary outcomes are listed below.

To investigate the maternal outcome:

1. To assess the development of maternal complications in women with previous unexplained/unexplored fetal demises, in particular the development of hypertension related complications and diabetes mellitus.

2. To determine the impact on the health service (hospital stay, induction of labour rate, caesarean section rate for both patients that receive induction and those that go into spontaneous labour).

To investigate the impact on fetal outcome:

1. To assess the total number of admissions of newborn neonates to the neonatal unit or intensive care unit.

2. Birth weight of babies.

3. Apgar score of all these babies.

3.6 Study size

Stillbirth is a relative rare pregnancy outcome, but as Tygerberg hospital is the sole referral hospital in the eastern side of the Cape Town metropolitan area, enough numbers could be obtained to make a meaningful conclusion. As this was an audit to
determine the safety of an already implemented hospital protocol, the primary endpoint is binomial (in this case fetal mortality). Using a power of 80% and alpha of 0.05, the audit required at least 57 women to demonstrate that the stillbirth rate of women in the study is at least the same as the general population; using a general (world-wide) population stillbirth risk of 5 per 1000 and a risk for women with a prior stillbirth 10 times that (5%). However, the stillbirth rate in the Tygerberg drainage area is much higher - 2.45%; and the recurrence risk not known. If the recurrence rate is taken as a modest 4 times higher than in the general population, the same number (57) of women needed to be included in the audit.

3.7 Statistical methods

Chi-squared and Fisher's exact tests were used for the comparison of frequencies. For comparison of means and medians the Student t test and Mann–Whitney test, were used respectively. Epinfo and Microsoft Excel were used for statistical analysis. A p value of <0.05 was regarded as significant.

3.8 Ethics

Approval for the prospective cohort study was obtained from the Stellenbosch University Health Research Ethics Committee (HREC S11/11/045). As patients are managed according to standard departmental obstetrics policies and protocols, a waiver of informed consent was obtained from the Ethics Committee. The audit was an anonymous folder review and data was not linked to patient identity and thus patient privacy and confidentiality was completely protected.
4. Findings and Analysis

4.1 Participants

During the audit period, 306 patients were referred to the institution with a previous intra-uterine fetal death for further management. It was not possible to determine the number of patients that should have been referred (as per provincial policy), but who remained at district level of care due to non-adherence to policy. Of the referred patients, 161 had a definite cause for the previous IUD and they could be managed clinically according to their specific disease and were excluded from the audit.

Table 1 shows the etiology of these previous stillbirths as identified either from a good history and/or from previous clinical notes or histology results.
Table 1: Etiology of previous stillbirths as determined from history and/or clinical notes or available histology

<table>
<thead>
<tr>
<th>Pathology/ Disease entity</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abruptio placentae</td>
<td>53</td>
<td>32.92</td>
</tr>
<tr>
<td>Two or more previous IUDs</td>
<td>17</td>
<td>10.56</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>15</td>
<td>9.32</td>
</tr>
<tr>
<td>Placental insufficiency (either clinical or histological)</td>
<td>15</td>
<td>9.32</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>13</td>
<td>8.07</td>
</tr>
<tr>
<td>Syphilis</td>
<td>6</td>
<td>3.73</td>
</tr>
<tr>
<td>Severe growth restriction</td>
<td>6</td>
<td>3.73</td>
</tr>
<tr>
<td>Intrapartum deaths</td>
<td>5</td>
<td>3.11</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>4</td>
<td>2.48</td>
</tr>
<tr>
<td>Previous IUD related to twin pregnancy</td>
<td>4</td>
<td>2.48</td>
</tr>
<tr>
<td>Termination of pregnancy (for preeclampsia, severe IUGR) PPROM</td>
<td>4</td>
<td>2.48</td>
</tr>
<tr>
<td>Chronic villitis</td>
<td>3</td>
<td>1.86</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>2.48</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
<td>1.86</td>
</tr>
<tr>
<td>Cord prolapsed</td>
<td>2</td>
<td>1.24</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>2</td>
<td>1.24</td>
</tr>
<tr>
<td>Perivillous fibrin deposition with severe villitis and intervillitis</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td>Chromosomal abnormalities</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td>Maternal cardiac (during cardiac surgery)</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td>Postdates</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>161</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>
Of the remaining patients, 145 were identified as having a previous unexplained/unexplored stillbirth where no definite or suspected reason could be identified. Nine patients met exclusion criteria (see Table 2) and there were 2 protocol violations (patients defaulted follow-up at Tygerberg hospital).

**Table 2: Exclusion criteria from audit**

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Numbers</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twins in index pregnancy</td>
<td>4</td>
<td>44.44</td>
</tr>
<tr>
<td>Known diabetes</td>
<td>3</td>
<td>33.33</td>
</tr>
<tr>
<td>Known diabetes and hypertension</td>
<td>1</td>
<td>11.11</td>
</tr>
<tr>
<td>Known severe restrictive lung disease</td>
<td>1</td>
<td>11.11</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Forty-two of these study patients (with no known previous medical problems) developed complications during their antenatal course that necessitated a change in clinical management and earlier (<39 weeks) delivery.

Table 3 shows these complications. The 2 patients that developed an abruption, was respectively 28 weeks and 4 days and 29 weeks and 1 day pregnant. They had an uncomplicated antenatal care follow up until sudden IUD’s secondary to abruption.
Table 3: Complications that necessitated earlier delivery in patients with previous intra-uterine fetal deaths

<table>
<thead>
<tr>
<th>Complication during antenatal course</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes mellitus</td>
<td>20</td>
<td>47.62</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>10</td>
<td>23.81</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>3</td>
<td>7.14</td>
</tr>
<tr>
<td>Pregnancy induced hypertension</td>
<td>3</td>
<td>7.14</td>
</tr>
<tr>
<td>Abruptio placentae</td>
<td>2</td>
<td>4.76</td>
</tr>
<tr>
<td>Severe intra-uterine growth restriction</td>
<td>1</td>
<td>2.38</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>1</td>
<td>2.38</td>
</tr>
<tr>
<td>Preterm labour (PPROM)</td>
<td>1</td>
<td>2.38</td>
</tr>
<tr>
<td>Chorioangioma of the placenta</td>
<td>1</td>
<td>2.38</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>42</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

There remained 92 study patients with a previous unexplored/unexplained stillbirth that had an uncomplicated antenatal course and were managed according to the policy of routine induction of labour at term. Although the protocol change was to move from routine induction at 38 weeks to term (>39 weeks), the decision on the exact timing of delivery (39 weeks/273 days or 40 weeks/280 days) were left to the attending clinician. Seventy women were planned for delivery at 40 weeks; and 18 for delivery at 39 weeks. Of the remainder, 1 patient refused induction of labour, 1 were planned for 41 weeks and two defaulted their induction admission date. This is shown in Figure 1.
Figure 1: Flow diagram of study patients

Patients referred with a previous IUD
n=306

145 patients qualified for study

Patients included in final audit
n=92

70 planned for induction at 40 weeks

18 planned for induction at 39 weeks

1 refused induction of labour

Patients that developed complications during antenatal care requiring earlier delivery
n=42

1 refused induction of labour

1 mistakenly planned for induction at 41 weeks

Excluded (met exclusion criteria)

n=9

Protocol violations (follow-up defaulters)

n=2

Patient with a known cause for IUD excluded from the audit
n=161
The two patients that were excluded due to protocol violations, were patients that attended the high risk clinic and met inclusion criteria, but did not deliver at Tygerberg. The 2 patients that defaulted their induction of labour date were included in the study as they did deliver at Tygerberg and outcome data on them was available.

4.2 Descriptive data

Table 4 describes the booking characteristics of the population group.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gravidity</th>
<th>Parity</th>
<th>Ectopic</th>
<th>Miscarriage</th>
<th>TOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (or median)</td>
<td>29.4</td>
<td>(3)</td>
<td>(2)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>Range</td>
<td>19-41</td>
<td>2-7</td>
<td>1-6</td>
<td>0-2</td>
<td>0-3</td>
<td>0-1</td>
</tr>
</tbody>
</table>

The mean gestational age at booking was 17 weeks and 6 days (range: 4 weeks and 2 days - 37 weeks and 3 days).

Figure 2 shows the health status of the study group. Most of the patients were healthy at booking. Seven patients were known with HIV disease and already on highly active antiretroviral treatment; 5 patients were known with hypertension of which 4 was on chronic treatment; 2 patients were on TB treatment and another 2 patients were on treatment for asthma. One patient was known with epilepsy.
The booking RPR, Rh blood group and RVD status characteristics of the study population is shown in Table 5.

**Table 5: Booking blood characteristics of patients at booking**

<table>
<thead>
<tr>
<th>Status</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPR</td>
<td>3*</td>
<td>89</td>
</tr>
<tr>
<td>Rh blood group</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>RVD (mean CD4 385, range 108-809)</td>
<td>18†</td>
<td>74</td>
</tr>
</tbody>
</table>

*Only two patients were adequately treated

†7 patients were already on HAART; 7 were initiated on HAART early in pregnancy, and 4 were started on PMTCT during pregnancy.
Smoking was quite prevalent in the study population with 19.57% of women indicating that they were smoking in pregnancy. 13.4% of patients consumed alcohol and there were no active drugs/substance abusers in the group.

The social habits of patients are shown in Figure 3.

![Social habits of patients at booking](image)

**Figure 3**: Social habits of patients at booking

### 4.3 Follow-up of patients during antenatal care

The mean time that a patient waited for referral to Tygerberg Hospital (from date of booking until 1\textsuperscript{st} appointment at Tygerberg) was 31.6 days (range 1 day - 255 days).

The mean gestation (in days) at referral was 156.7 (22 weeks and 2 days) and range was 6 weeks and 2 days to 39 weeks and 5 days.

The protocol stated a screening Doppler at 24 weeks; and 88 patients (95.6%) had such a test. The mean gestational age at which screening Doppler was done, was 27 weeks and 3 days (range 21 weeks and 5 days - 38 weeks). Twenty-five patients
(28.4%) needed a repeat Doppler for a RI of 75 - 95%. No screening Doppler was abnormal (>95\textsuperscript{th} percentile).

The protocol further stated that a diabetic screen should be done at 28 weeks. Sixty-four patients (69.57%) had such a screen and the mean age such a screen was done, was 29 weeks and 3 days (range 13 weeks and 1 day – 37 weeks and 6 days).

4.4 Outcome: Maternal

4.4.1 Spontaneous labour vs induction of labour rate

Of the 92 patients in the audit, 47 (51%) went into spontaneous labour before their induction date. The mean gestation for onset of spontaneous labour was 272 days (38 weeks and 6 days) and the average birth weight for this group was 3157.3 gram (range 2220g–4680g).

By sub-analysing this same group, of the 70 patients who were planned for induction of labour at 40 weeks, 41 (58.5%) went into spontaneous labour and only 3 (16.6%) of the group planned for induction at 39 weeks. There is no difference in outcome whether induction was planned for 39 weeks or 40 weeks - most patients went into spontaneous labour just after 39 weeks. Ten patients delivered before 266 days (38 weeks), with the earliest gestation at 246 days (35 weeks and 1 day); all 10 went into spontaneous labour. The mean birth weight for this pre-term group was 2741 grams (range 2300-3810g).

Table 6 shows the breakdown of gestational age at delivery and the birth weight of the babies.
Table 6: Breakdown of gestational age at delivery

<table>
<thead>
<tr>
<th></th>
<th>Total group (n=92)</th>
<th>IOL planned at 39 weeks (n=18)</th>
<th>IOL planned at 40 weeks (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual gestation at delivery</td>
<td>39 weeks and 2 days</td>
<td>39 weeks and 1 day</td>
<td>39 weeks and 2 days</td>
</tr>
<tr>
<td>Gestation at delivery when spontaneous onset of labour occurred</td>
<td>38 weeks and 6 days</td>
<td>38 weeks and 6 days</td>
<td>38 weeks and 4 days</td>
</tr>
<tr>
<td>Gestation at delivery when IOL was performed</td>
<td>39 weeks and 6 days</td>
<td>39 weeks and 1 day</td>
<td>40 weeks and 1 day</td>
</tr>
<tr>
<td>Birth weight at delivery: mean (and range) in grams</td>
<td>3167 (2220-4680)</td>
<td>3170 (2170-3670)</td>
<td>3147 (2220-4680)</td>
</tr>
</tbody>
</table>

Gestational age was determined according to current protocol, by correlating the dates from the last menstrual period with the early ultrasound. When there was sure dates that correlated within one week of the early scan in the 1st trimester; or within 2 weeks according to the second trimester scan, the dates according to the LNMP was used. When the dates were uncertain or not known, the gestational age was calculated using the earliest formal ultrasound available. All the patients underwent sonar evaluation at referral; for 73% of women (n=66) this occurred before 24 weeks of gestation. Of the remaining 26 patients; 13 patients were referred only in the third trimester without any early ultrasound or accurate dates and the clinicians dealing with them dated them according to the late ultrasound. Of the other 13 patients, 10 had accurate dates that corresponded with the late ultrasound and the rest were
dated according to the late ultrasound and the clinical estimate at first booking. This is depicted in Figure 4.

It is interesting to note that of the 47 patients who went into spontaneous labour, 38 were early bookers (before 24 weeks; some as early as 4 weeks; all had detail scans) and the other 9 patients booked in the early third trimester and were dated according to late ultrasound (all before 31 weeks). In fact, the gestational age as calculated by dates (and not the actual sonar EDD) were used for only 6 patients. If the gestational age is recalculated for all using the ultrasound EDD, the mean gestation for spontaneous delivery in this group is 38 weeks and 5.5 days.

**Figure 4: Gestation calculation**
4.4.2 NVD vs Caesarean section rate

Of the 47 women planned for induction of labour, but who went into spontaneous labour, only 6 were delivered with a Caesarean section, 5 for fetal distress and 1 for prolonged spontaneous rupture of membranes with unsuccessful attempts at induction of labour.

Induction of labour was performed in the remaining 45 patients. Twenty (44.44%) of the 45 women that were admitted for induction of labour had a Caesarean delivery. For six of the cases, the indication given in the folder was fetal compromise (fetal distress during labour). Four were due to poor progress, 1 for a failed induction and 9 were scheduled (elective) Caesarean sections for obstetrical reasons. Figure 5 shows the caesarean section rate in each group as well as the reasons for caesarean section in the induction group.

Figure 5: Caesarean section rate and reasons for Caesarean section in each group
There was a higher risk for any CS in the induction of labour group (RR 2.27; 95% CI 1.5-3.4; p<0.05) and also a higher risk for emergency CS in the induction of labour group (RR 1.9; 95% CI 1.16-3.1; P <0.05).

4.4.3 Admission-to-Hospital – Start-of-Induction Time

The mean time from admission-to-hospital to start-of-induction time was 22 hours, ranging from 50 minutes to 72 hours. The most common reason for the delay in start of the actual induction was due to patient overload in the acute labour ward, delaying non-urgent inductions. Induction was defined as started with the first administration of prostaglandin (if cervical ripening was needed); or with rupture of membranes or placement of a catheter bulb. In cases of elective caesarean section as method of delivery, induction was taken as the time from which the anaesthetic commenced. Only 15 patients were started with induction on the day of admission, 13 on the next day and 17 women only on the third day since admission.

4.4.4 Start-of-induction – Delivery time

The mean time from start-of-induction of labour until delivery was 26.7 hours (range: 0.25 - 152.92 hours). For 15 women, the total induction-delivery took more than 27 hours and the longest induction took 153 hours until delivery. Figure 6 shows the number of patients delivering before 24 hours, between 24 and 48 hours, 48 and 72 hours and more than 72 hours from induction time.
Figure 6: Respective timeframes from induction of labour to delivery

4.4.5 Delivery-to-discharge time: Normal vertex delivery and caesarean section respectively

The delivery-to-discharge time for the normal vertex deliveries and the caesarian sections were also calculated. This was done in order to give an idea of any delays and if it was related to any complications that developed intrapartum or postpartum. The normal vertex deliveries (n=66) delivery-to-discharge time was 22.17 hours (range 5.17 – 93.5 hours). There was one patient with a cervical tear (with postpartum hemorrhage) and one patient that had intrapartum shoulder dystocia with a subsequent third degree tear that needed to be sutured in theatre.

The caesarian sections (n=26) mean delivery-to-discharge time was 62.87 hours (range of 35.63 – 91.87 hours). There was one intra-operative complication. This was related to an adherent placenta. Fortunately no hysterectomy was required. One patient developed post-operative wound sepsis (which was managed medically) from a caesarian section that was done for poor progress.
4.4.6 Admission-to-Discharge time: Comparison between spontaneous labour vs. induction of labour for patients with normal vertex deliveries

The average admission-to-discharge time for the 41 patients who went into spontaneous labour and delivered normal were 26.47 hours. The average admission-to-discharge times for the 25 patients who underwent an induction and delivered normal were 70.8 hours. There was a significant ($p<0.001$) difference in admission-to-discharge time between the patients who went into spontaneous labour and those who underwent induction and had normal vertex deliveries.

4.5 Outcome: Fetal

The next section will briefly discuss the neonatal outcome and admissions.

All babies from the 92 cases included in the audit were born alive, with a median 5-minute Apgar score of 9 (range 8-10). Only 4 babies needed admission; the rest were discharged with their mothers. None needed ICU admission. The reasons for admission as well as the duration of admission are shown in Table 7. The mode of delivery is also shown.
Table 7: Reason and duration for admissions of newborns

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Reason for admission</th>
<th>Duration of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section (Elective - prior obstetrical indication)</td>
<td>Transient tachypnoea of the newborn</td>
<td>48 hours</td>
</tr>
<tr>
<td>Caesarean section (Breech)</td>
<td>Meconium aspiration syndrome</td>
<td>24 hours</td>
</tr>
<tr>
<td>Caesarean section (Severe condylomata)</td>
<td>Hydronephrosis on antenatal scan, daily monitoring of renal function until mother was discharged</td>
<td>72 hours</td>
</tr>
<tr>
<td>Normal vertex delivery</td>
<td>Phototherapy</td>
<td>48 hours</td>
</tr>
</tbody>
</table>
5. Conclusion

5.1 Summary of Findings

Although the primary aim of the study was not to determine the causes of previous IUD’s, it is important to note that abruptio placentae still remain the leading cause of intra-uterine fetal demise in this population (32.93%). Chorioamnionitis is also very prevalent (10.56%) and it is concerning that there are still IUD’s related specifically to syphilis (3.73%). Hypertensive disease in pregnancy and its other related complications (apart from abruptio) will rank third.

Of the 145 patients that could potentially qualify for the study, 42 (28.97%) needed earlier delivery. The main reasons for earlier delivery were the development of diabetes mellitus (47.62%) and preeclampsia (23.81%). Patients with previous unexplained/unexplored stillbirth are thus at increased risk of complications in subsequent pregnancies and there is a need to follow them up in an environment with properly trained staff and at least at regional (specialist) hospital level of care.

Antenatal care should focus aggressively on the screening for diabetes and hypertensive-related conditions and complications of pregnancy. It is an issue of concern that the screening for diabetes was not optimal in the final study population (only 69.57% of the audit population was screened) in light of the fact that this was indeed the main reason for earlier delivery.

The population included a wide age spectrum of patients (19-41 years) and only 17 (18.48%) were known with chronic diseases. HIV remains the most prevalent chronic condition (7.6%) in the population. The adherence to the protocol in terms of doppler and diabetic screening (95.6% and 69.57% respectively) was not optimal.
In terms of maternal outcome the key findings were as follows: 51% of the total study population went into spontaneous labour before their induction of labour date. There was no difference in outcome whether induction was booked at 39 or 40 weeks, most patients went into spontaneous labour before 39 weeks. The emergency caesarean section rate in the IOL group was nearly twice as high as in the spontaneous labour group.

There were significant delays in the admission-to-hospital to start-of-induction time (15 patients started induction within 24 hours, 13 patients between 24 and 48 hours and 17 patients after 48 hours). At a current cost of R2300 per night for a patient in a secondary level hospital, this equates to quite a significant amount. Actual induction time in a labour ward further adds to these costs. The complication rate for the entire cohort can be regarded as minimal if the delivery–to–discharge time is taken into consideration as well as the fact that there were only 2 complications in each group. As expected, patients who received an induction of labour and had a normal delivery (in comparison with women who went into spontaneous labour and had a normal vertex delivery), stayed almost three times longer in hospital.

In terms of fetal outcome the most important findings are as follows: All the babies were born alive with a median Apgar score of 9. The birth weights ranged from 2400 grams to 4680 grams. There were no intensive care admissions; 4.35% of babies were admitted briefly and all of them were discharged within 72 hours.

### 5.2 Limitations

According to the Western Cape Metro East protocol, all patients with a previous IUD must be referred to Tygerberg hospital. It may have been that patients that should have been referred remained at district level. Unfortunately, the outcome of those
patients is not included in the study and it would be difficult to predict how their outcome would have influenced our results. However, the numbers should be limited as referral systems is very well developed and adhered to in the metropolitan area.

Many systems used to classify stillbirths do not distinguish between cases where no cause of death was found despite thorough investigation and those where incomplete investigation made final diagnosis impossible. This last group is likely to represent a large proportion of unexplained stillbirths. However, in South-Africa, clinicians are often confronted with this scenario and we have to accept the cause as unknown although another explanation which might alter the management of the subsequent pregnancy might exist.

5.3 Interpretation and conclusion

As far as we are aware, this is the first prospective cohort study following women up after a previous unexplained/unexplored stillbirth according to a specific protocol.

Careful follow up at a high risk clinic identifies new or concealed maternal or fetal complications in 29% of patients with a previous IUD and no obvious maternal or fetal disease in the index pregnancy. It remains a high risk pregnancy, but with careful follow-up and exclusion and management of complications, the fetus may be safely delivered at term.

It is not possible in the hospital population to clearly separate the unexplained from the unexplored stillbirths, especially if delivery took place elsewhere and notes are not available and patients rarely know what investigations was done. For this reason the unexplored IUDs are included in the hospital protocol; the audit suggest that this may be warranted.
This change in policy is very relevant to the Western Cape population and would most certainly be applicable to other third world countries where resources are limited. It has been shown previously that unexplained stillbirth is much more prevalent in patients with a poor social-economic background and this research will contribute to the management of these pregnancies in resource-limited countries.

5.4 Future research

The safety of the protocol will be continued to be monitored using the perinatal problem identification system (PPIP).

6. Funding

No source of funding was obtained for this study
Appendix A: Protocol for management of a patient with a previous unexplained/unexplored IUD
TYGERBERG HOSPITAL
Department of Obstetrics and Gynaecology: General Specialist Services

PROTOCOL FOR THE MANAGEMENT OF A
PREVIOUS UNEXPLAINED OR UNEXPLORED INTRA-UTERINE DEATH

A. INTRODUCTION

- While the majority of women with a previous stillbirth have a live birth in the subsequent pregnancy, they are a high-risk group with an increased incidence of adverse maternal and neonatal outcomes.
- A previous unexplained intra-uterine fetal death (IUFD) is an indication for evaluation at a specialist maternity unit in the subsequent pregnancy.
- There have been no studies that adequately tested fetal benefit from intervention by routine induction of labour with a previous unexplained IUFD.
- There is little evidence-based data to guide the treating clinician in the antepartum surveillance of a patient who had a prior unexplained stillbirth.
- Any decision to proceed with early delivery (before 40 weeks) to prevent stillbirth must incorporate an understanding of the increased risks of maternal and neonatal complications compared with the potential benefits.
- Deliveries before 39 weeks of gestation are associated with an increased risk of admission to neonatal special care units for respiratory complications and other neonatal morbidities.

B. DEFINITIONS AND ABBREVIATIONS

- **IUFD: INTRA-UTERINE FETAL DEATH**

  ‘A still birth is a death prior to the complete expulsion or extraction from its mother of a product of conception; the death is indicated by the fact that after such separation the fetus does not breathe or show any evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of the involuntary muscles.’

  - For the purpose of this protocol, a gestational age of IUFD after 24 weeks (or 500 grams birth weight if uncertain gestation) is used.

- **Unexplained IUFD:** An IUFD where previous notes are available, and despite investigations that may include placental histology, no cause for the IUFD could be found.

- **Unexplored IUFD:** An IUFD where no previous notes are available or no attempt was made to investigate the death.
C. MANAGEMENT: PATIENT WITH PREVIOUS IUFD ≥ 24 WEEKS

- Obtain all the information pertaining to the loss and all other obstetric and medical history. Ensure ALL notes are reviewed, even from other hospitals.
- If a clearly identifiable, non-repeatable cause is found (e.g. syphilis, cord prolapse, chorioamnionitis, shoulder impaction, intra-partum asphyxia etc.) and the current pregnancy is healthy, manage the patient at the correct level of care (MOU or district hospital).
- If a clear diagnosis for the IUFD was made, manage the patient accordingly (e.g. previous documented abruptio, hypoxaemia due to placental dysfunction, severe maternal disease etc.)
- If no clear cause can be found, and the history is not indicative of abruptio placentae, manage further according to this protocol:

D. MANAGEMENT: INITIAL ASSESSMENT AND WORK-UP OF PREVIOUS UNEXPLORED/UNEXPLAINED IUFD

- Ensure routine care, booking bloods, HIV results, dating scans etc. are checked.
- Re-enforce to the parents that the previous event was not under their control and that they should bear no guilt for that occurrence.
- Emphasise the importance of regular clinic attendance and that no additional antenatal surveillance tests are needed when there is normal placentation in the index pregnancy.
- Give advice that there is no evidence that a scheduled early delivery (before 39 weeks) leads to better outcome, but that there is enough evidence to show harm. Counsel the patient to receive elective induction of labour at term (>39 weeks).
- Do a routine detail scan at 18-22 weeks. If anomalies found, manage accordingly.
- Do a routine screening for diabetes at booking and again at 28 weeks.
- Do umbilical artery Doppler at 24 weeks and manage according to the result.
- If the placental function test (Doppler) is normal, and there is good fetal growth, the pregnancy can be managed at general specialist level up to 39 weeks.
- Admit for planned delivery (induction of labour) at >39 weeks gestation (use the TBH Induction of Labour protocol).
- Be aware that there may be a higher incidence of postpartum depression in a mother who has lost a baby before.
This protocol replaces all related preceding protocols

<table>
<thead>
<tr>
<th>AUTHORISED BY</th>
<th>GS Gebhardt</th>
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<tbody>
<tr>
<td>COMMITTEE RESPONSIBLE</td>
<td>Protocol Discussion Group, Tygerberg Hospital.</td>
</tr>
<tr>
<td>DATE REVISED</td>
<td></td>
</tr>
<tr>
<td>DATE EFFECTIVE</td>
<td>1 January 2012</td>
</tr>
<tr>
<td>REVIEW DATE</td>
<td>31 May 2014</td>
</tr>
<tr>
<td>EVIDENCE</td>
<td>Evidence basis for the above decisions is available on request</td>
</tr>
</tbody>
</table>

Signed: GS Gebhardt

Head: general specialist services, Obstetrics and Gynaecology
Appendix B: Ethics committee approval

Approval Notice
New Application

24-Jan-2012
OBERHOLZER, Leena

Protocol #: S11/11/045
Title: Delivery after a previous unexplained intrauterine fetal death beyond 24 weeks: Audit of a change in policy from induction at 38 weeks to induction at 40 weeks gestation.

Dear Dr Leena OBERHOLZER,

The New Application received on 21-Nov-2011, was reviewed by members of Health Research Ethics Committee 1 via expedited review procedures on 20-Jun-2012 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: 24-Jun-2012 - 24-Jun-2013

Please remember to use your protocol number (S11/11/045) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to: set further questions, seek additional information, require further modifications, or suspend the conduct of your research and the consent process.

After Internal Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/ethics and should be submitted to the Committee before the year has expired.
The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number projects may be selected randomly for an external audit.

Translation of the consent document in the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB000538

The Health Research Ethics Committee complies with the SA National Health Act No 81 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Mrs Claudette Abrahams at Western Cape Department of Health (healthres@health.westerncape.gov.za) or Dr Helen Visser at City Health (helm.visser@capetown.gov.za) or 021 400 3981). Research that will be conducted at any tertiary academic institute requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard REC forms and documents please visit www.sun.ac.za/ethics

If you have any questions or need further help, please contact the REC office at 0219389457.

Included Documents:
Protocol
CV
Checklist
Declaration
References


