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ORIGINAL ARTICLE

Chance of healthy versus adverse outcome in subsequent pregnancy after previous loss beyond 16 weeks: data from a specialized follow-up clinic

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ABSTRACT

Purpose: Women with a previous fetal demise have a 2–20 fold increased risk of another stillbirth in a subsequent pregnancy when compared to those who have had a live birth. Despite this, there is limited research regarding the management and outcomes of subsequent pregnancies. This study was conducted to accurately quantify the chances of a woman having a healthy subsequent pregnancy after a pregnancy loss.

Methods: A retrospective study was conducted at a tertiary-level unit between March 2019 and April 2021. We collected data on all women with a history of previous fetal demise attending a specialized perinatal history clinic and compared the risk of subsequent stillbirth to those with a normal pregnancy outcome. Outcome data included birth outcome, obstetric and medical complications, gestational age and birth weight and mode of delivery. Those who had healthy subsequent pregnancies were compared with those who experienced adverse outcomes.

Results: A total of 101 cases were reviewed. Ninety-six women with subsequent pregnancies after a history of fetal demise from 16 weeks were included. Seventy-nine percent of women ($n = 76$) delivered a baby at term, without complications. Overall, 2.1% had repeat pregnancy losses ($n = 2$) and 2.1% delivered babies with fetal growth restriction ($n = 2$). There were no cases of abruption in a subsequent pregnancy. Eighteen neonates were delivered prematurely (18.4%), 15 of these (83.3%) were due to iatrogenic causes and three (16.7%) were spontaneous. In univariable logistic regression analyses, those with adverse outcomes in subsequent pregnancies had greater odds of pre-eclampsia (Odds ratio *(OR) = 3.89, 95% CI = 1.05–14.43, $p = .042$) and fetal growth restriction (OR = 4.58, 95% CI = 1.41–14.82, $p = 0.011$) in previous pregnancies compared to those with healthy outcomes. However, in multivariable logistic regression analyses, neither variable had a significant odds ratio (OR = 2.03, 95% CI = 0.44–9.39, $p = .366$ and OR = 3.42, 95% CI = 0.90 – 13.09, $p = .072$ for pre-eclampsia and FGR, respectively).

Conclusion: Four in five women had a healthy subsequent pregnancy. This is a reassuring figure for women when contemplating another pregnancy, particularly if cared for in a specialist clinic.

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Stillbirth; fetal demise; recurrence; pregnancy loss

Introduction

Over the past two decades, many high-income countries have reduced stillbirth rates [1,2]. Nevertheless, the UK has plateaued, ranking poorly at 33rd of 35 high-income European countries [1]. Recent MBRRACE-UK figures report an annual stillbirth rate of 3.51 per 1000 total births [3,4]. Experiencing stillbirth leaves an enduring psychological burden on families. Despite discrepancies in gestational age limits and stillbirth definitions, many lessons regarding care and prevention are applicable to second-trimester loss also [5].

Stillbirth encompasses many losses including that of the baby, as well as hopes for parenthood and self-esteem, and can lead to a fear of never having

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another child [6]. A systematic review found parents reported several negative emotional and psychological symptoms following stillbirth [7–9].

Subsequent pregnancies after stillbirth lead to increased physical and emotional anxiety [10]. Psychological distress can persist with parents reporting worry, panic attacks and depression [11]. A repeat stillbirth is the most dreaded outcome.

The literature on stillbirth recurrence is inconsistent. Some report a recurrence risk between two and twenty-fold, yet others highlight no increased risk [12–16]. There is a five-fold increase in the odds of repeat stillbirth when the cause is known [1]. However, in unexplained stillbirth there is no consensus on subsequent risk. According to postmortem studies, the etiology in half of all cases is undetermined making it more difficult to counsel [17].

Some studies have found increased risks of prematurity, low birth weight, placental abruption and medical interventions in pregnancies following stillbirth whilst others report no such risks [10,13,18–20]. A seminal Scottish retrospective study with 364 patients found significantly increased risks of pre-eclampsia, placental abruption, and low birth weight [12]. Similarly, Keren et al. showed pregnancies after stillbirth had increased incidences of hypertension and diabetes [21].

A paucity of information remains regarding subsequent healthy pregnancy outcomes after stillbirth. Research has focused on the risk of recurrent complications but no single figure regarding this simple, yet critical statistic has emerged. Whilst Keren et al. found almost 77% of women deliver a live baby in their subsequent pregnancy, this figure included babies born with conditions linked to placental complications e.g. fetal growth restriction [21].

This study aimed to assess the risk of subsequent stillbirth and report outcomes in subsequent pregnancies in a diverse cohort of women attending a specialized follow-up clinic after previous intrauterine fetal death.

Materials and methods

Design

We conducted a retrospective single-center cohort study to evaluate the risk of subsequent stillbirth in women with a history of pregnancy loss at 16 weeks gestation or later, who were booked for maternity care between March 2019 and April 2021.

Setting

All data collection was conducted at the unit's dedicated "Perinatal History Clinic". The observed cohort was derived from two computerized databases: Ultrasound software and the Electronic Health Record (EHR). Women deemed high-risk due to prior pregnancy outcomes are referred at booking visits. Information in the databases entered prospectively by the consultant responsible includes detailed medical and obstetric information. After every consultation, relevant details and scans are reported on an ultrasound database and uploaded onto the EHR.

Inclusion criteria

We included all women with a pregnancy loss before 31 March 2019 and who then had a subsequent pregnancy and delivered between 31 March 2019 and 1 April 2021. We excluded those without adequately documented previous pregnancies. The study included both second and third-trimester losses. The latest pregnancy monitored in the specialized clinic was analyzed. In women with multiple previous fetal demises, the most recent loss was also taken for analysis. It was not a requirement for the index fetal demise to have occurred at the unit.

Data collection

A patient list was generated and crossmatched across databases. Ninety-six women met the inclusion criteria.

Outcomes

Medical and obstetric data were collected for the subsequent pregnancy and subdivided into: maternal risk factors, index fetal demise details, management and outcome in the subsequent pregnancy managed in the clinic. We collected data on known maternal risk factors; maternal age (at booking), BMI, existing diabetes mellitus and hypertensive disorders, smoking, patient chromosomal abnormalities, and evidence of poor obstetric history. Emphasis was placed on previous pregnancy complications including abruption, fetal growth restriction and preterm birth.

Information regarding previous fetal demise and investigations performed to identify the cause were recorded. A systematic work-up to identify the cause of demise was completed if the event occurred at the unit. This involved fetal autopsy and placental

histopathology. When the cause of death was certain, the cause fell into categories allocated according to the Causes of death and associated conditions (Codac) classification [22].

We collected data on the management of antenatal care, prophylaxis and/or treatment during the subsequent pregnancy. Primary surveillance for women with a previous demise comprised of first-trimester PAPP-A level and second-trimester uterine artery Doppler (UtA) (PI). A low PAPP-A in this study was defined as a maternal serum PAPP-A value <0.45 MoM and a combined UtA PI > 2.5 was considered elevated and indicative of potentially abnormal placental blood flow. Any medications and dosages prescribed during the index pregnancy were collected.

We collected data on the subsequent pregnancy focusing on placental complications: placental abruption, fetal growth restriction (FGR)*, preterm birth (before 37 weeks of gestation), repeat fetal demise.

Healthy neonatal outcomes were defined as appropriately grown neonates delivered at term ($\geq$37 weeks).

*FGR was a clinical diagnosis for the purposes of this study and was not dependent exclusively upon birth weight and/or gestational age. These included cases with a normal birthweight after arrest or deceleration in estimated fetal weight or abdominal circumference.

An appropriately grown neonate delivered at term was defined as a baby born without the adverse outcomes mentioned. Women who had healthy outcomes were those who gave birth to a term-grown neonate. Analysis between the groups was performed. Secondary outcomes included pre-eclampsia, gestational diabetes and hypertension.

Statistical analysis

Data was analyzed using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Numerical variables that were normally distributed were summarized with the mean (standard deviation) and by the median (min-max) otherwise categorical variables are expressed as frequencies and percentages. Categorical data were compared in those with healthy and adverse outcomes using the Fisher exact test and numerical variables were compared using the Mann–Whitney *U* test. Univariable logistic linear regression analysis was conducted to determine variables associated with an adverse outcome and those variables that were significant at the 5% level were included as covariates in a multivariable linear logistic model. A significance level of 0.05 was used for all hypothesis tests.

Ethical approval

This was approved as a service evaluation of the Perinatal History Clinic. All data was routinely collected and held under NHS data protection regulations and were anonymized, kept confidential and only accessible to the research team.

Results

One hundred and one women met the inclusion criteria, five were excluded due to loss to follow-up ($n = 2$), termination following Spina Bifida diagnosis ($n = 1$) and limited clinical information ($n = 2$).

The population studied was composed of 96 patients. Most women experienced fetal loss in the third trimester ($n = 63$, 65.6%) and 17.7% ($n = 17$) occurred in the final month of pregnancy (37–42 weeks).

According to Codac classification, 61/96 (63.5%) women had a previous fetal demise of unknown cause. However, 37 women had unknown causes of a previous IUFD despite extensive investigations taking place whilst, in the remaining 24 cases, no investigations occurred.

Three previous fetal demises were due to chronic histiocytic intervillositis. Of six demises secondary to infection, four were due to preterm pre-labor rupture of membranes and two were due to parvovirus. There were two losses due to fetal causes secondary to twin-to-twin transfusion.

A placental cause of demise was determined for example when fetal death was associated with fetal growth restriction, placental abruption, or the presence of large or multiple infarcts on histology. Of 17 cases with placental causes, 13 were due to FGR and four were due to placental abruption. There were six cord-related demises. The one congenital anomaly was a diaphragmatic hernia. There were no intrapartum causes of demise.

Subsequent pregnancies of the 96 patients were followed up. Neonatal outcomes were as follows:

The mean birth weight of all neonates was 2837.28 g $\pm$ 598.075 SD and the mean gestational age at delivery was 37.5 weeks.

Among the cohort, two gave birth to live twins, making the total number of neonates born 98. However, one set of twins was born prematurely at 36 weeks of gestation and thus were included in the

figure of those born preterm. Conversely, 76 women (78.6%) delivered healthy neonates at term.

Adverse neonatal outcomes occurred in 20 (20.8%) women. Seventeen women experienced preterm birth (and eighteen neonates delivered prematurely) and two had fetal growth restriction (2.1%). In one case, a woman delivered a baby who was preterm and growth restricted. One woman delivered a baby who was preterm, growth-restricted and suffered from pre-eclampsia at delivery.

Two women had a recurrent perinatal loss (2.1%). Both cases were pregnancy losses before 24 weeks. Further details of these recurrent cases are shown in the Appendix. There were no cases of placental abruption in the subsequent pregnancy.

Of the 18 preterm births (18.4%), 15 (83.3%) were iatrogenic preterm deliveries, two (13.3%) had an induced vaginal delivery, eight (53.3%) had an elective cesarean delivery and four (26.7) had emergency cesarean delivery whilst the remaining three had SVDs. Of note, the earliest preterm birth was 32 weeks and 4 days gestation.

Overall, 76 (79.2%) women comprised the healthy group whilst 20 (20.8%) women had adverse outcomes. Baseline characteristics are shown in Table 1.

A total of 29 (30.2%) women had adverse maternal outcomes. Twenty-two (22.9%) women were diagnosed with GDM, four (4.2%) had gestational hypertension and three (3.1%) had pre-eclampsia. Of these three cases, one was diagnosed with pre-eclampsia in a previous pregnancy.

Despite 76 women having healthy pregnancy outcomes, one was diagnosed with pre-eclampsia at 25 weeks. Two women in the adverse outcome group had more than one existing complication during their pregnancy including pre-term birth, pre-eclampsia and fetal growth restriction concurrently.

Women with adverse outcomes in their subsequent pregnancy had higher rates of previous placental complications as is depicted in Table 2. More women who suffered adverse outcomes had been diagnosed with pre-eclampsia (univariable logistic regression Odds Ratio (OR)=3.89, 95% CI = 1.05–14.43 $p = .042$) and fetal growth restriction (univariable logistic regression OR = 4.58, 95% CI = 1.41–14.82, $p = .011$) in previous pregnancies. These figures show that the odds of adverse outcomes are approximately 4 times greater in those with pre-eclampsia and nearly five times greater in those with growth restriction. However, in a multivariable logistic regression analysis, these factors were no longer statistically significant with $p = .366$ (OR = 2.03, 95% CI = 0.44−9.39) and $p = .072$ (OR = 3.42, 95% CI = 0.90−13.09) for pre-eclampsia and fetal growth restriction, respectively. This lack of significance is due to the strong association between pre-eclampsia and FGR leading to collinearity in the multivariable model, compounded by the fact that there are only a few adverse outcomes. A quarter of women in the adverse outcome group had a history of prior pre-eclampsia compared to 7.9% of those with healthy outcomes. More than a third of women in the adverse outcome cohort had previously delivered a fetal growth-restricted baby and preterm birth was more common.

Sixteen women were found to have experienced an additional loss (16–23 weeks). Of these, two (10%) were from the adverse group and fourteen (18.4%) were from the healthy group.

During the subsequent pregnancy, medication was prescribed based on previous history, and other factors (PAPP-A, UtA Dopplers and BMI). Most women (79.2%) were prescribed aspirin and 26 women were prescribed LMWH. A higher percentage of women were taking medication in the adverse group. Among

Table 1. Baseline characteristics in women with healthy outcomes compared with women with adverse outcomes in their subsequent pregnancy.

Characteristic	Healthy outcome (*N*=76)	Adverse outcomes (*N*=20)	*p* Value
Median maternal age (years) & range	35 (20–45)	34.5 (22–55)	MW .48 =*P*
Ethnicity: white	32 (42.1)	10 (50.0)	
Other white background	10 (13.2)	1 (5.0)	
Black or black British	16 (21.1)	6 (30.0)	
Mixed background	4 (5.3)	0 (0.0)	
South Asian or south Asian British	9 (11.8)	3 (15.0)	
Any other Asian background	4 (5.3)	0 (0.0)	
Any other ethnic group	1 (1.3)	0 (0.0)	
Median BMI (kg/m^2 (range))	25.9 (17.8–30.1)	26.1 (15.7–35.5)	MW .903= *P*
Current smokers	2 (2.6)	2 (10.0)	.191
Diabetes mellitus	0 (0.0)	0 (0.0)	
Hypertensive disorders	4 (4.2)	2 (10.0)	.601
Genetic abnormalities	0 (0.0)	0 (0.0)	

Data are counts (%) or median and range. MW: Mann Whitney.

Table 2. Previous adverse maternal and obstetric complications with an emphasis on placental complications.

Previous obstetric and maternal complication	Healthy outcome (N= 76)	Adverse outcome (N= 20)	p Value (Fischer)
Pre-eclampsia	6 (7.9)	5 (25.0)	.048*
Preterm birth	5 (6.6)	1 (5)	>.999
Fetal growth restriction	8 (10.5)	7 (35)	.014*
Placental abruption	8 (10.5)	5 (25.0)	.136
Fetal vascular malperfusion	2 (2.6)	0 (0.0)	>.999
Placental villous dysmaturity	2 (2.6)	0 (0.0)	>.999
Pprom	4 (5.3)	1 (5.0)	>.999
Miscarriages <15w	34 (44.7)	6 (30.0)	.310
Miscarriages 16–23 w[a]	14 (18.4)	2 (10.0)	.510
Recurrent (>3)	9 (11.8)	3 (15.0)	>.999
Chronic histiocytic intervillositis (chi)	3 (3.9)	2 (10.0)	.278
Intrahepatic cholestasis of pregnancy	0 (0.0)	0 (0.0)	
Antiphospholipid syndrome (aps)	3 (3.9)	1 (5.0)	>.999
HELLP	2 (2.6)	0 (0.0)	>.999
Other thrombophilia	3 (3.9)	0 (0.0)	>.999

Data are counts (%).
[a]Figure does not include the previous IUFD.
*p Value is statistically significant at <.05.

the 76 participants who were given aspirin, in 18 (23.7%) of them it was started after an abnormal uterine artery Doppler at the second-trimester ultrasound. These women had only been referred to the clinic after this finding. Notably, a larger proportion of women (30.0%) in the adverse group were prescribed LMWH during their pregnancy than those in the healthy group (26.3%), which proved not to be statistically significant.

Women in the adverse outcome group were also numerically more likely to have low PAPP-A scores (10%) when compared to women with healthy outcomes (3.6%). However, this was not statistically significant ($p = .28$). Of the two women with low PAPP-A scores in the adverse outcome group, both had a preterm birth. All women who had low PAPP-A were given aspirin and no patient developed pre-eclampsia.

Twenty-four (42.9%) patients from the healthy group had UtA Doppler scores above 2.5Pi compared to only four (20.0%) women in the group with adverse outcomes. This difference was not statistically significant ($p = .311$).

Discussion

These findings contribute to the body of evidence regarding subsequent pregnancy following fetal demise. Of great significance is the finding women can be assured of encouraging outcomes, with approximately 80% of babies delivered at term without complications. This figure is higher than that identified by Keren et al. who report 68% of women delivered a baby appropriate for gestational age. Reasons for this include varying populations; many women in the Israeli study were referred to a high-risk clinic based on multiple risk factors, suggesting possible referral bias. Their cohort had a high prevalence of prothrombotic risk factors [23,24]. In addition, differences in care pathways may play a role. Although studies quoted refer to varying gestational ages, it was a pragmatic decision to review losses in this study from 16 weeks onwards.

Our fetal demise recurrence rate (2.1%) was lower than described in larger studies [13,25]. One study of 73 subsequent pregnancies had a higher rate of 6.8% [21]. A possible explanation is that upon referral to specialist clinics patients received substantial antenatal care, increased surveillance, earlier prophylactic treatment, and a protocol to consider delivery between 37 and 39 weeks, compared to previous pregnancies. Considering this, larger controlled studies in a similar clinic setting are needed to precisely assess the prognosis of individual pregnancies after IUFD.

Furthermore, in our cohort of women, unexplained fetal loss accounted for 38.5% of all previous fetal loss. Such findings are in line with the literature, demonstrating that the percentage of demise with unclassified causes ranges from 12 to 50% [26–28]. In addition, with placental causes being the second most common etiology for previous fetal demise in our study, this corroborated with other studies ranking placental abnormalities as the second leading cause [29–31].

Although the rate of recurrent fetal loss was low, over 20% of subsequent pregnancies were complicated by preterm birth and fetal growth restriction. Preterm birth was among the most common complication noted, affecting 18.4% of neonates. However, it is important to note that 83.3% of preterm deliveries were due to medical intervention which suggests that

prematurity in women with previous fetal loss is rarely spontaneous. Potentially, high rates of iatrogenic preterm birth in the study group result not only from obstetric complications but also from patient/carer anxiety. It is important to note that whilst our study defined a late preterm birth (35–36 weeks) as an adverse outcome, this may not be perceived as such by women anxious of recurrent stillbirth.

Two women delivered babies with growth restrictions in their subsequent pregnancies. Both had normal PAPP-A at 12 weeks and received prophylactic aspirin (150 mg) early. A systematic review of aspirin in 1317 women with abnormal UtA Dopplers found that aspirin commenced before 16 weeks reduces the incidence of pre-eclampsia and SGA [32]. Late initiation of aspirin could also explain the three cases of pre-eclampsia in subsequent pregnancies as these women started aspirin late [33].

Amongst those with previous fetal loss secondary to FGR ($n = 13$), one experienced repeated FGR. Surkan et al. demonstrated history of SGA in a previous pregnancy is significantly linked to an increased risk of demise in subsequent pregnancies [34]. Indeed, women in our study with an adverse outcome in subsequent pregnancy had significantly higher FGR rates. The literature supports this with small studies showing the risk of adverse perinatal outcomes is increased in women with a previous demise related to placental insufficiency [20,21,35].

The role of pre-eclampsia was also significant with those who had an adverse outcome having more complications of pre-eclampsia in prior pregnancies. Giannubilo et al. found women with previous pre-eclampsia had increased rates of preterm birth in subsequent pregnancies [36]. This may partly explain the relationship between the high rates of previous pre-eclampsia and high preterm birth rates in the following pregnancy. Our finding was a recurrence rate of 9% [37]. Only one of 11 women had repeated pre-eclampsia: a lower figure than existing studies [38–41]. One large registry-based cohort of 500,000 women found the risk of pre-eclampsia in the second pregnancy was 25.2% [39]. The high proportion of patients receiving prophylactic aspirin in our study (79.2%) may explain these differences. Moreover, 100% adherence to daily intake is pro-actively encouraged.

Strengths and limitations

The strength of this study lies in reduced recall bias as all information was recorded in two digitalized databases in real-time. For missing data, other database areas were searched, and missing information was clarified with clinicians. This study employed comprehensive search methods to identify the complete cohort. These methodological strengths allowed us to clearly define groups and remove ascertainment bias. The unit's specialist clinic is one of few dedicated services that care for women in a subsequent pregnancy after IUFD. Excellent models of multidisciplinary continuity of care coupled with frequent review are associated with improved outcomes and better overall patient experience [42].

Our primary limitation was the small number of women, limiting some of the statistical analysis for group comparisons and making it difficult to conclude the applications to larger populations. This was a single-center study, subsequent outcomes may have been improved compared to other centers. Given the retrospective nature of the study, the sample size and details about the pregnancy were dependent on accurate and complete prior documentation. Finally, as this was a non-randomized study, there was limited ability to guarantee the comparability of the two groups.

Implications for clinical practice and policy

This is one of a small number of studies providing a single figure for counselling women contemplating a new pregnancy and assessing their subsequent pregnancy outcome when cared for in a dedicated center. Although the figure obtained does not address individualized cases, it is a reassuring statistic that can be relayed to patients in a dedicated perinatal history clinic whilst considering other factors.

We found a lower risk of recurrence of IUFD than previously reported. This can be used to reassure women. Nevertheless, women should still be made aware of the possibility of pre-eclampsia, fetal growth restriction and especially the high likelihood of iatrogenic preterm delivery in subsequent pregnancies.

Much work remains to improve fetal demise investigations and correctly classify loss as 25% of cases had had no investigations. This lack of crucial information can cause elevated levels of concern, for parents and obstetricians [42]. To be able to accurately inform parents of future risks, priority must be given to establishing causes of fetal death, especially as perinatal outcomes differ in subsequent pregnancies according to the cause of previous loss [43]. This will enable more precise counselling for what can be such a heterogeneous event.

Future research

A cross-regional study over a longer period would allow an analysis of our research questions in a larger sample size. Individual patient data meta-analysis which focuses on overall positive outcomes, not merely the clinician-driven recurrence of complications would be beneficial for counselling.

Conclusion

In conclusion, these findings should provide comfort to couples who experienced fetal loss after 16 weeks and are contemplating another pregnancy. Their overall prognosis is favorable with low recurrence levels. However, a high number of adverse obstetric outcomes remains. It is vital these women are cared for in dedicated clinical settings. Further research is needed to assess the varying risk factors between those who have healthy outcomes and adverse outcomes in their subsequent pregnancy.

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Ethical approval

As this was a service review, no ethical approval was needed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix. Explanation of recurrent IUFD

Table A1. Women who had recurrent IUFD further explained.

IUFD cases	Previous IUFD		Subsequent IUFD	
Patient 1	Mother: 26 years of age, G1P0, 28 weeks of gestation, boy, 912 g, died in utero		Mother: 36 years of age, BMI 30,8, G5P3, PAPP-A 0.6995, 20 weeks of gestation, girl, 154 g, died in utero	
	Cause of death	Considered unknown, evidence of placental insufficiency with placental abruption	Cause of death	Unexplained
	Management	Aspirin 75 mg	Management	Aspirin 75 mg
Patient 2	Mother: 53 years of age, G0P0, 23 weeks of gestation		Mother: 54 years of age, G1P0, PAPP-A 1.2815, 19 weeks of gestation, boy, 320 g, died in utero	
	Cause of death	Pregnancy loss following chronic PV bleeding throughout 1st and 2nd trimester secondary to sub-chorionic hematoma, with PPROM and subsequent significant antepartum hemorrhage	Cause of death	Early rupture of membranes; PPROM, with severe chorioamnionitis
	Management	Aspirin 150mg, Labetalol	Management	Labetalol
	Obstetric history	Advanced maternal age, IVF donor egg donor sperm, essential hypertension		