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Subsequent pregnancy outcomes following second trimester miscarriage—A prospective cohort study

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ABSTRACT

Objectives: Pregnancy after second-trimester miscarriage represents as clinical challenge. This study sought to determine the rates of recurrence, preterm birth and live births in a cohort of 185 women with previous second-trimester miscarriage. We hypothesized that there would be a higher rate of second-trimester miscarriage and preterm birth in subsequent pregnancy after second trimester miscarriage. The primary objectives of this study were to establish rates of second-trimester miscarriage, preterm birth and live births in this cohort. Secondary objectives were to examine medical and surgical interventions, in addition to other pregnancy outcomes and complications.

Study design: This was a prospective cohort study carried out in a tertiary referral center in southern Ireland with over 8000 deliveries per year. 175 women were followed up. Inclusion criteria were an ultrasound confirmed second-trimester miscarriage between June 2009 and June 2013 and subsequently having a pregnancy between July 2009 and January 2016. Fifty-five women did not become pregnant during the study period and were excluded. Ten women were excluded for missing data.

Results: Between July 2009 and January 2016, 110 women became pregnant following a previous second-trimester miscarriage. In total, 81 babies were born to 77 mothers. The recurrence rate of second-trimester miscarriage was 6.3% (7/110) and the preterm birth rate was also 6.3% (7/110). The cesarean section rate was 45%. Including those who experienced first or second trimester miscarriage, 47% (78/155) of those who were followed up did not go on to have a live infant.

Conclusions: Women experiencing second-trimester miscarriage are at increased risk in subsequent pregnancies of recurrence. Second-trimester miscarriage needs to be highlighted as a risk factor for adverse pregnancy outcomes. Greater research into its pathophysiology is required to advance preventative measures.

Introduction

Second-trimester miscarriage (also termed second-trimester pregnancy loss, 'late' miscarriage, or mid-trimester loss) is defined as pregnancy loss after the 12th and before the 24th week of gestation [1]. In a low-risk population, the risk of miscarriage in the second trimester approaches 0.5% [2]. Three clinical presentations of second-trimester miscarriage predominate; intrauterine demise (IUD), preterm labor (PTL) and preterm premature rupture of membranes (PPROM). Vaginal bleeding or abdominal pain can feature in all three processes [3]. Ascending infection is a frequent accompaniment. A recent study examining the morbidity associated with second-trimester miscarriage found that 64.6% of cases were attributable to IUD, 17.7% to PPROM and 17.9% to PTL [4]. Known contributors to second-trimester miscarriage include cervical insufficiency, fetal and placental anomalies, uterine malformations, chromosomal abnormalities and genetic and acquired thrombophilias [1].

Pregnancy after second-trimester miscarriage presents a clinical challenge [1,5]. In specific circumstances with a clearly identifiable etiology of pregnancy loss such as cervical insufficiency, recurrence may be predictable, but this is rarely the case [6]. Indeed, a second-trimester miscarriage often has multiple potential causes [1,7–9], Investigation of second-trimester miscarriage is often incomplete, and frequently the unavailability of perinatal pathology precludes post-mortem examination at early gestations. Conversely, there may be no evident cause found despite appropriate investigation in up to half of cases [10]. In a woman

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who experiences more than one second-trimester loss, differing causal factors can predominate at different gestations in each pregnancy [1]. Furthermore, recurrence rates are affected by factors not amenable to change by the clinician, such as race, low socioeconomic or educational status, marital status and maternal age and modifiable risk factors such as body mass index (BMI) and smoking [11].

There is a paucity of information available with which to counsel women on pregnancies following a previous second-trimester miscarriage. Much of the published literature focuses on recurrent first-trimester miscarriage [12], preterm birth [8,13], or stillbirth [14]. The lack of an international consensus on definition of a stillbirth [15] leads to a significant overlap between these groups when reported [8,13,16,17], resulting in few well-defined second-trimester cohorts.

A recent study demonstrated that second-trimester miscarriage carries a recognized risk of maternal morbidity and mortality, particularly if complicated by hemorrhage or sepsis [4]. We aimed to follow up this distinct cohort of women who experienced second-trimester miscarriage into their subsequent pregnancies. The primary objectives of this study were to establish rates of second-trimester miscarriage, preterm birth and live births in this cohort. Secondary objectives were to examine medical and surgical interventions, in addition to other pregnancy complications.

Materials and methods

This study followed a cohort of women who had experienced second-trimester miscarriage between June 2009 and June 2013 as part of an earlier retrospective cohort study [4].

Our institution is a tertiary-referral university hospital, with approximately 8000 deliveries annually, serving a rural and urban population. An amendment to the preceding ethical approval from the Clinical Research Ethics Committee of the Institutional Teaching Hospitals was submitted and approval for a prospective cohort study was granted (Ref no: ECM 3 (w) 03/03/15 & ECM 4 (h) 01/10/13).

The original study had strict inclusion and exclusion criteria based on gestational age, ultrasound findings and clinical presentation [4]. Second-trimester miscarriage was defined as pregnancy loss between 13 + 0 and 23 + 6 weeks, with a fetus weighing less than 500 g [18]. It identified 181 cases of second-trimester miscarriage and provided a cohort of 175 women (six women experienced two second-trimester miscarriages during this study) [4].

The women were followed-up prospectively in the period July 2009-January 2016 in observation of any subsequent pregnancies. Antenatal attendances were confirmed on the hospital patient management system (Citrix IPM) and medical charts obtained postnatally. Demographic and clinical data were obtained from individual chart review. Data included age, body mass index (BMI), obstetric history, medical history, surgical history, as well as investigations, interventions, management and outcomes of the current pregnancy. The outcomes most relevant to second-trimester miscarriage were recurrent second-trimester miscarriage and preterm birth (except where delivery was close to term and iatrogenic or specific risk factors existed such as multiple pregnancy). Descriptive analyses were used to evaluate the sample. All analyses were carried out using Microsoft Excel, version 16.0.7167.2055.

Results

Of the 175 women who were followed-up, ten women had missing or unobtainable medical notes. Fifty-five (55/165; 33%) women from the original cohort did not become pregnant in the study period. The average age in this group was 34.6 years (SD: 5.2). There were 15 nulliparous and 40 multiparous women. Four underwent documented fertility investigations at our hospital.

Between July 2009 to January 2016, 110 women became pregnant. The demographics of the women who became pregnant are presented in Table 1. Maternal age ranged from 16 to 49 years, with a mean age of 32.5 years (SD: 5.8 years). The mean BMI was 27.2, (SD: 5.5). One third of women (38/110; 34%) were nulliparous. There were no common medical co-morbidities, but 10 women (9%) had a history of depression. A presentation with an IUD was the most common loss type in the index second-trimester miscarriage (72/110; 65%). Four women had undergone in-vitro fertilization treatments and one woman had taken clomiphene for ovulation induction. Twenty-six women had a first-trimester miscarriage. Of those with an ongoing pregnancy, most women booked for antenatal care at 10–13 weeks' gestation (54/84; 64%), 20% (16/84; 19%) booked at less than 10 weeks and 14 (14/84; 17%) were booked after 13 weeks. Thirteen underwent serial cervical length ultrasound surveillance (13/84; 15%). Eleven women (11/84; 13%) had a cerclage inserted – seven cervical and four abdominal.

In their first pregnancy following a second-trimester miscarriage, 77 women delivered 81 healthy infants (77/110; 70%), whereby there were 72 singleton pregnancies and five sets of twins (Fig. 1). There was a single intrauterine death at 22 weeks' gestation in one set of twins secondary to severe early onset intrauterine growth restriction. Their mother (A) is included in the second-trimester miscarriage cohort for all other analyses. Seven pregnancies in the cohort ended in a second-trimester miscarriage, details of which are outlined in Table 2.

Nine women (9/84; 9.5%) were delivered prior to 37 weeks' gestation. One woman was electively induced at 36 + 6 weeks for a history of previous abruption at 37 weeks and a second woman with DCDA twins labored spontaneously at 36 + 5. These women are not included with the seven women who had a preterm birth in Table 3.

One woman (B) presented with premature rupture of membranes and contractions at 23 + 3 weeks with a footling breech presentation. As the estimated fetal weight was >500 g, the decision was made for delivery by classical cesarean section. Despite resuscitation efforts, the neonate died at four minutes of life. As the birthweight was 560 g, this is registered as a neonatal death per Irish legislation [18]. This woman is included in the preterm birth group for analysis.

Of the 76 women with a pregnancy of over 24 weeks' gestation who gave birth to a live infant (excluding patient A), 23 were induced (23/76; 30%). Indications for induction included past obstetric history (11/23; 47.8%), small for gestational age (3/23; 13%) ruptured membranes (3/23; 13%), post-term (2/23; 9%), hypertension (2/23; 9%) and pelvic girdle pain (1/23; 4.3%). Of these, 6 (6/23; 26%) were over 40 weeks' gestation.

There were 35 spontaneous vaginal deliveries (35/76; 46%), 34 lower segment cesarean sections (34/76; 45%) and seven instrumental deliveries (7/76; 9%). There were 24 elective caesarean sections (24/34; 71%) and 10 emergencies (10/34; 29%). The overall emergency cesarean section rate amongst those in labor (n = 40) was 25% (10/40; 25%). There were 15 women with one previous cesarean section eligible for trial of labor. The trial of labor rate in this group was 20% (3/15; 20%) with one woman delivering vaginally.

There were 26 first-trimester miscarriages. These diagnoses consisted of 12 missed miscarriages, 5 incomplete and 9 complete miscarriages. The mean gestation of miscarriage was 6 + 6weeks (range 4 + 5–12 + 6 weeks, n = 22). Almost half occurred at 7–12 + 6 weeks' gestation (12/26; 42.3%), while 38.5% (10/26) occurred below 7 weeks' gestation. Four women (4/26; 15.3%) had

Table 1
Maternal socio-demographic factors and medical history, stratified by pregnancy outcome.

Pregnancy >37/40 %(n=70) [*]		Preterm <37/40 %(n=7)	Second Trimester Loss % (n=7)	First Trimester Loss %(n=26)
Age				
<20	1.4 (1)	14.3 (1)	0 (0)	3.8 (1)
20-29	25.7(18)	14.3 (1)	0 (0)	23.1 (6)
30-39	69 (48)	71.4(5)	71.4 (5)	57.7 (15)
>40	4.3 (3)	0 (0)	28.6 (2)	15.4 (4)
Race				
Irish	85.7 (60)	57.1 (4)	57.1 (4)	84.6 (22)
European	7.1 (5)	0 (0)	28.6 (2)	11.5(3)
African	5.7 (4)	28.6 (2)	14.3 (1)	0 (0)
Asian	1.4 (1)	14.3 (1)	0 (0)	3.8(1)
BMI kg/m2				
Underweight (<18.5)	1.4 (1)	0 (0)	0 (0)	Data Unavailable[**]
Normal (18.5-24.9)	34.2 (24)	57.1 (4)	57.1 (4)	
Overweight (25-29.9)	40 (28)	14.3 (1)	14.3 (1)	
Obese >30	18.5 (13)	28.6 (2)	14.3 (1)	
Missing Data	5.7 (4)	0 (0)	14.3 (1)	
Smokers	8.5 (6)	0(0)	0 (0)	0 (0)
Other Adverse Pregnancy Outcomes				
Stillbirth	1.4 (1)	0 (0)	0 (0)	0 (0)
>3 1 st Trimester Loss	4.3 (3)	0 (0)	0 (0)	11.5 (3)
>1 2nd Trimester Loss	7 (5)	14.3(1)	28.6 (2)	11.5 (3)
Previous term pregnancy	76 (53)	42.9 (3)	57.1 (4)	73 (19)
Previous Cesarean Section	27 (19)	28.6 (2)	28.6 (2)	7.6 (2)
Index 2nd Trimester Loss Type				
IUD	66 (46)	42.9 (3)	57.1 (4)	73 (19)
PTL	14 (10)	14.3 (1)	0 (0)	3.8 (1)
PPROM	18.6(13)	42.9 (3)	42.9 (3)	23 (6)
Missing Data	1.4 (1)	0 (0)	0 (0)	0 (0)
Index Loss to Pregnancy Interval				
Mean (n Months (SD))	13.9 (14.4)	9.1 (7)	7.4 (4.4)	13.9 (9)
Medications in Pregnancy				
Folic Acid	91.4 (64)	71.4 (5)	85.7 (6)	30.7 (8)
Aspirin	54.3 (38)	42.9 (3)	28.6(2)	26.9 (7)
Low Molecular Weight Heparin	11.4 (8)	14.3 (1)	0 (0)	73.6 (2)
Progesterone	15.7 (11)	14.3 (1)	28.6 (2)	3.8 (1)
Cerclage				
Abdominal	4.3 (3)	14.3 (1)	0 (0)	0 (0)
Cervical	7.1 (5)	14.3 (1)	14.3 (1)	0 (0)

[*] All figures referred to as % (n) unless otherwise stated.
[**] Data not routinely collected in early pregnancy patients.

chemical pregnancies. The mean age in this group was 33.5 years (range 16–44) and average parity was 1.24 (SD: 1.1). Including those who experienced first or second trimester miscarriage, the total number of women without a live birth in the study period was 78 (78/165; 47%).

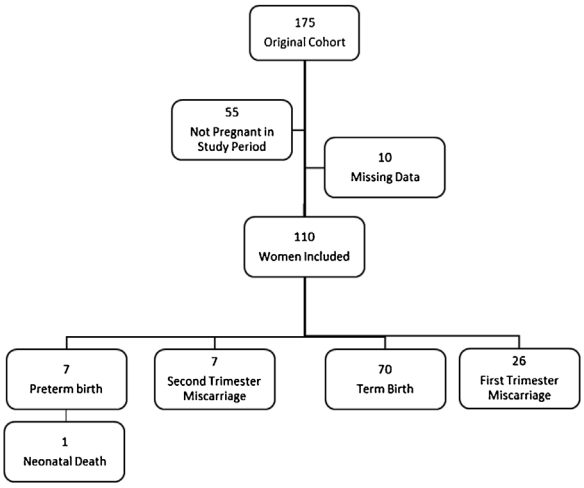

Fig. 1. Outcome of first pregnancies following second trimester loss.

Comment

This study examined subsequent pregnancy outcomes in 175 women who had experienced second-trimester miscarriage. Among 110 women who became pregnant in the study period 2009–2016, the recurrence rate of second-trimester miscarriage was 6.3% and the preterm birth rate was also 6.3%. The first-trimester miscarriage rate was 24%. Most women had a successful first pregnancy following second-trimester miscarriage with 81 babies born to 77 mothers (77/110; 70%). Thirteen percent of women required cerclage (11/84; 13%) - seven trans-vaginal and four abdominal. The cesarean section rate was 45% in those with pregnancies over 24 weeks' gestation.

This is a well-categorized cohort with prospective follow-up in a single hospital by a single group of researchers. Few defined cohorts of this size exist within the literature. Women of different nationalities and social backgrounds in rural and urban areas across Southern Ireland are included. We included second-trimester miscarriage by all modalities, that is PPROM, PTL and IUD. We examined rates of first-trimester miscarriage in addition to secondary outcomes such as cesarean section and induction rates, which are seldom investigated [14].

The lack of a national patient database means that follow-up excepted women who had further pregnancies outside of our hospital. Fertility care in Ireland remains predominantly in the private sector and patients may have undergone fertility

Table 2
Women Experiencing Recurrent Second Trimester Miscarriage.

Age		Nationality	Parity	Index Loss Type	Gestation of Index Loss	Loss Type This Pregnancy	Gestation	Singleton/ Multiple Pregnancy	Fertility Treatment	Medication	Interventions
1	39	Irish	4+1	IUD1	16/40	IUD	15/40	Singleton	No	Folic Acid	None
2	36	Irish	2+1	IUD	14/40	IUD	17/40 (14/40 size)	Singleton	No	Folic Acid, Aspirin	None
3	41	Nigerian	2+3	1xPTL2 1x IUD 1xPPROM3	13/40 18/40 19+6/40	PPROM	20/40	Singleton	No	Aspirin, Progesterone	Cervical length, McDonald cerclage
4	36	Irish	2+1	IUD	19/40	IUD	18/40 (14/40 size)	Singleton	No	Folic Acid	None
5	40	French	0+1	PPROM	21/40	PPROM	18/40	DCDA4 Twins	IVF5	Folic Acid	Intravenous antibiotics
6	33	Spanish	0+1	PPROM	18/40	PPROM	16/40	Singleton	No	Folic Acid, Progesterone	Cervical cerclage
7	31	Irish (A)	0+1	IUD	22/40	IUD	22/40	DCDA Twins	No	Nil	Cervical Length, Serial Growth US6

Intrauterine Demise.
Preterm Labour.
Preterm Premature Rupture of Membranes.
Dichorionic Diamniotic.
In-Vitro Fertilisation.
Ultrasound.

Table 3
Women Experiencing Preterm Birth.

Age		Parity	Nationality	Type of previous loss	Gestation of previous loss	Gestation at delivery	Singleton/ Multiple	Reason for delivery	Intervention/ complication
1	22	0+2	Irish	2 x PPROM1	21/40 x 2	28+6/40	Singleton	Fulminating Pre-eclampsia	Emergency C/S2 Abdominal cerclage in situ
2	17	0+1	Irish	IUD3	18/40	31+4/40	Singleton	Spontaneous	Admitted for cervical shortening- abdominal cerclage in situ
3	39	0+3	Irish	PTL4(twins) IUD Singleton	22+6 20/40	34+2/40	Singleton	IUGR5, AEDF6	Elective C/S
4	34	2+1	Irish	IUD	18/40	36+4/40	Singleton	SROM7, Meconium Grade 2, (2 previous C/S)	Emergency C/S
5	32	0+1	Nigerian	PPROM	22/40	27+3/40	DCDA8 Twins	PPROM at 27+2, chorioamnionitis	Cervical cerclage inserted at 18/40, Emergency C/S
6	31	1+1	Thai	PPROM	15/40	35+5/40	Singleton	Spontaneous	Cervical surveillance
7	36	3+1	Angolese	IUD	22/40	23+3/40	Singleton	Spontaneous	PTL, footling breech, Emergency Classical C/S RIP at 4 mins

Preterm premature rupture of membranes.
Caesarean section.
Intrauterine demise.
Preterm labour.
Intrauterine growth restriction.
Absent end diastolic flow.
Spontaneous rupture of membranes.
Dichorionic diamniotic.

investigation and treatment elsewhere. The number of women with adverse outcomes or interventions is low. There is a potential for misinterpretation of complication rates based on these outcomes. The absence of a control group as in other studies [15] is a limitation as it is not possible to draw significant comparisons. Confinement to a single hospital means outcomes were potentially influenced by adherence to local guidelines.

Our cohort of 110 women compares favorably with the published literature. Edlow et al. had a cohort of 97 women with pregnancy loss between 14 and 23 + 6 weeks, but the subsequent pregnancy outcomes of just 30 women were examined [1]. Goldenberg studied 90 women experiencing loss between 13–24 weeks', but the study is over 30 years old and neonatal survival rates are not comparable [5]. Other studies included stillbirth [19], periviable delivery up to 28 weeks[6 8] or termination of pregnancy [20]. These larger studies were based on national databases and not individual chart reviews.[6 8 20]

Our live birth rate was 46% (76/165; 46%). The survival rate was 98% with one neonatal death. Goldenberg reported a live birth rate of 89% with 39% of infants born prematurely [5]. Edlow et al had a 73% live birth rate, 45% of these infants were preterm [1]. Frias et al reported a birth rate of 24% but included women with prior miscarriage and stillbirth [17]. McPherson et al also reported a lower birth rate compared to controls [19].

We report a second-trimester miscarriage recurrence rate of 6.3% and a preterm birth rate of 6.3% also. While our recurrence rate appears low, it is 12 times the internationally recognized primary occurrence rate for second trimester miscarriage of 0.5%.[5] Edlow reported a recurrence rate at 27% with a preterm birth rate of 33% [1]. Similarly, other studies demonstrated recurrence rates of 3.1–7% with preterm birth rates of 30–36% [8,19,20], Additionally, McPherson showed that among those women with second-trimester loss or stillbirth, second-trimester miscarriage was more likely in their subsequent pregnancy than a stillbirth [19]. This echoes studies which demonstrate that recurrent miscarriage, stillbirth and preterm birth are associated with adverse outcomes in subsequent pregnancies such as PPROM and preterm delivery [14,21,22].

Of those experiencing recurrent second-trimester miscarriage, 70% (5/7) had experienced at least one miscarriage after 18 weeks. In the preterm group this rose to 86% (6/7; 86%). Goldenberg showed a 62% preterm birth rate in those with an index loss at 19–22 weeks [5]. The Preterm Prediction Study demonstrated that prior spontaneous preterm delivery at 23–27 weeks' gestation was most highly associated with early spontaneous preterm delivery (<28 weeks' gestation) in a subsequent pregnancy [23]. PPROM and preterm labor were significantly associated with recurrence [23]. Monson et al found that a history of preterm birth preceding a pregnancy complicated by PPROM was associated with recurrent preterm birth [24].

Roberts et al noted that following a 14–19 weeks index loss, an interpregnancy interval (IPI) of ≤3 months had an increased risk of recurrence and that for all index losses, an IPI of >18–24 months increased the risk of recurrence [20]. Edlow found that IPI had no significant impact on those with previous second-trimester miscarriage or preterm birth but that in those with previous term delivery an IPI of < 6 months increased risk of preterm birth or miscarriage tenfold. [1]. In our cohort, we found that IPI was shortest in the preterm birth and second-trimester miscarriage groups (Table 1).

The Cesarean section rate was high in this cohort at 45% (34/76). The elective repeat Cesarean rate was 70% (24/34), with 26% (20/76) of women having had at least one previous Cesarean section. Additionally, there was a low uptake of VBAC. Black et al showed a similar increase in both elective and emergency Cesarean section rates in a cohort with previous stillbirth [14]. The induction rate was high at 29.5%. More work is needed to determine if decisions regarding mode and timing of delivery are physician- or patient-led and what additional factors contribute to these decisions. Second-stage cesarean section has been associated with a two-fold increase in preterm birth in subsequent pregnancies and investigation into an association with second-trimester miscarriage is merited [25].

The reassuring message is that most women have a successful pregnancy following a second-trimester miscarriage. The rate of recurrence and preterm birth is lower than previously quoted. There is a notable risk compared to the general population however, meriting close observation during pregnancy, particularly women with a history of periviable loss. These women are also susceptible to increased intervention. Policies should focus on improving selection criteria for cervical length monitoring, cervical cerclage insertion and increased attention paid to induction and delivery guidelines in this cohort. Screening for infection in those with prior PPROM should be routine at antenatal visits. There needs to be adequate provision for perinatal pathology training and expansion of services to allow full investigation of second-trimester miscarriage.

Identifying which women are more susceptible to poor outcomes is challenging. The relationship between stillbirth and second-trimester IUD is unclear. One can precede the other and it has been suggested the two should be considered together [19]. They are both implicated in preterm birth [17,18,21,22], Placental and perinatal pathology have a crucial role in furthering our understanding of this relationship and potentially reclassifying perinatal pregnancy loss [26]. Larger prospective studies are required to establish the recurrence risks and significance of each type of second-trimester miscarriage. Clinical and translational research must focus on the mechanisms of these, as well as confounding factors such as chorioamnionitis. Greater understanding may further development of preventative measures and better indicate when intervention is appropriate in this group.

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Conflict of interest

The authors declare that there are no conflict of interest.

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