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A review of reproductive outcomes of women with two consecutive miscarriages and no living child

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ABSTRACT

The definition of recurrent miscarriage ranges from two miscarriages according to the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology, to three consecutive pregnancy losses as defined by the Royal College of Obstetricians and Gynaecologists. Recent guidelines emphasise the need for further research on the effect of various recurrent miscarriage definitions on diagnosis, treatment and prognosis. Our study examines the management and pregnancy outcomes of nulliparous women attending Cork University Maternity Hospital's Pregnancy Loss Clinic, between 2009 and 2014, with their second consecutive first-trimester miscarriage. Information was sourced from the Pregnancy Loss Clinic's database, hospital patient management and laboratory systems, and clinical letters. 294 women were identified. A subsequent pregnancy was conceived by 82.3% (242/294) of women, with 72.7% (176/242) achieving a live birth. In conclusion, supportive care and selective medical management in dedicated pregnancy loss and early pregnancy clinics achieve excellent reproductive outcomes.

IMPACT STATEMENT

- **What is already known on this subject?** The definition of recurrent miscarriage is varied. It ranges from two miscarriages according to the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology, to three consecutive pregnancy losses as defined by the Royal College of Obstetricians and Gynaecologists. Recurrent miscarriage affects between 1 and 5% of women. Past studies suggest several causative factors, including epidemiologic, genetic, anatomical and endocrine. These factors may be identified in up to 50% of women with recurrent losses. Subsequent pregnancy outcomes are reported as excellent. However, recent guidelines focus on the need for further research on the effect of the various recurrent miscarriage definitions on diagnosis, investigation, treatment and prognosis.
- **What the results of this study add?** This study examined the management and pregnancy outcomes of women with two consecutive losses. A causative factor was identified in 29.3% of women in our cohort. A subsequent pregnancy was conceived by 82.3%, with 72.7% achieving a live birth. We suggest that supportive care is the single most effective therapy for women with two consecutive losses.
- **What the implications are of these findings for clinical practice and/or further research?** Over-investigation and empirical treatment should be avoided, with a greater emphasis placed on psychological support and risk factor modification in this group. Investigation protocols must be refined to only search for causes of recurrent miscarriage with evidence based treatment. Evaluation of supportive care in randomised control trials is needed.

KEYWORDS

Miscarriage; first trimester; investigation; reproductive outcomes

Introduction

First-trimester miscarriage is the commonest complication of pregnancy. It is defined as a spontaneous loss within the first 12 completed weeks. Miscarriage occurs in up to 20% of clinical pregnancies equating to approximately 14,000 miscarriages in Ireland per year (Health Service Executive 2014).

Recurrent miscarriage is variably defined. The definition ranges from two clinical miscarriages, according to both the

American Society for Reproductive Medicine (2013) and the European Society for Human Reproduction and Embryology (2017), to three consecutive pregnancy losses as defined by the Royal College of Obstetricians and Gynaecologists (2011). Approximately, 5% of women will experience two consecutive first-trimester pregnancy losses, while 1% will experience three consecutive losses (Practice Committee of the American Society for Reproductive Medicine 2012).

For expectant parents, any pregnancy loss can be a devastating event. It constitutes the end of a pregnancy and, for

Table 1. Causative factors for recurrent pregnancy loss.

Epidemiologic factors	Maternal age Number of previous miscarriages
Genetic factors	Parental chromosomal rearrangements Embryonic chromosomal abnormalities
Anatomical factors	Congenital uterine malformations
Endocrine factors	Diabetes mellitus Thyroid disease Polycystic ovarian syndrome
Immune factors	Anti-phospholipid syndrome
Inherited thrombophilic defects	Factor V Leiden gene mutation Prothrombin gene mutation Deficiencies of protein C/S and anti-thrombin III Methylenetetrahydrofolate reductase (MTHFR) mutation

many, the loss of a deeply desired future child (Neugebauer 2003). Couples are eager to be investigated with many requesting investigation, irrespective of clinical guidance (Meaney et al. 2016). A recent large-scale study reported that 78% of participants wanted to know the cause of their miscarriage, even if no intervention could have prevented it from occurring (Bardos et al. 2015).

Studies focussing on recurrent miscarriage have identified several causative factors, including epidemiologic, genetic, anatomical, endocrine and immune (Royal College of Obstetricians and Gynaecologists 2011; American Society for Reproductive Medicine 2012) (see Table 1). A typical evaluation includes a history and physical examination, testing for anti-phospholipid antibodies, thyroid function and diabetes. Other autoimmune and thrombophilic testing is often performed, but published studies have found the association with recurrent miscarriage to be modest (Royal College of Obstetricians and Gynaecologists 2011; American Society for Reproductive Medicine 2012; Bernardi et al. 2013). Following investigation, a putative diagnosis will be made in approximately 50% of women with recurrent pregnancy loss (American Society for Reproductive Medicine 2012).

Most published research suggests an excellent outcome of subsequent pregnancy in women with recurrent miscarriage (Clifford et al. 1997; Brigham et al. 1999). Women with idiopathic recurrent miscarriage can be counselled that the outcome of a subsequent pregnancy is excellent with supportive care, alone. Live birth rates can exceed 70%, depending on the maternal age and parity (American Society for Reproductive Medicine 2012). In women with the causative factors identified, pharmacological treatment is often recommended in addition to supportive care. Current suggested pharmacological treatment for anti-phospholipid syndrome and carriage of the factor V Leiden mutation appear to improve pregnancy outcomes, with live birth rates reported at 69% (Cohn et al. 2010) and 64% (Habayeb and Konje 2004), respectively.

The Pregnancy Loss Clinic at Cork University Maternity Hospital (CUMH) was established in 2008, and focuses on addressing both the emotional and medical needs of bereaved families in a dedicated specialist setting. Since 2009, the clinic has accepted women who have experienced two consecutive miscarriages. However, few existing studies have solely considered this significant population of women.

Recent guidelines highlight the need for further scientific research on the effect of various recurrent pregnancy loss definitions on diagnosis, prognosis and treatment (European Society for Human Reproduction and Embryology (ESHRE) Early Pregnancy Guideline Development Group 2017). By focussing on the group with two recurrent miscarriages, we aim to determine if current routine medical investigation in this population is helpful or even necessary, and whether their pregnancy outcomes are any different to those expected in the normal population.

Materials and methods

This retrospective cohort study took place in a tertiary level maternity hospital. All women attending the CUMH Pregnancy Loss Clinic, between January 2009 and December 2014, with their second consecutive miscarriage and who had no living child, were included.

The primary end-point was each woman's reproductive outcome in a subsequent pregnancy – namely live birth, miscarriage, ectopic pregnancy, stillbirth, termination and failure to conceive. The secondary end-points included the maternal characteristics, medical investigations performed and medical therapies initiated from the clinic visit.

A list of women who fulfilled the inclusion criteria was compiled following a detailed search of the Pregnancy Loss Clinic's database, and was checked against information recorded by the Pregnancy Loss Clinic Specialist Bereavement Midwives in their clinical diaries for completeness.

All of the information was entered manually into a database created on Microsoft Excel. The consultants' clinical letters and the Pregnancy Loss Clinic database were used to gather information including the maternal age, the maternal characteristics and the medical therapies initiated. The electronic hospital laboratory system was consulted for the results of investigations performed. Subsequent pregnancy outcome was determined using the electronic hospital patient management system. This provided information on each woman's subsequent clinic appointments and in-patient history at CUMH. All of the outcomes were cross-checked against the CUMH Early Pregnancy Clinic database, the Perinatal Mortality Database and clinical letters. Women were followed for a minimum of 18 months after their second miscarriage to identify any subsequent pregnancies.

Data analysis was performed using Microsoft Excel and GraphPad statistical analysis software (GraphPad, San Diego, CA). The descriptive statistics were derived to report all of the outcomes in the study population. Statistical comparisons were carried out by Fisher's exact test. The two-tailed value of $p < .05$ was considered to be statistically significant.

Results

Two hundred and ninety-four women with a history of two consecutive miscarriages and no living child were seen at the

CUMH Pregnancy Loss Clinic between January 2009 and December 2014.

Demographics

The mean maternal age at the time of the second miscarriage was 33.4 years (range: 16–46 years). Previously diagnosed medical conditions in this cohort included thyroid dysfunction, diabetes and deep vein thrombosis. 14.3% of women had a previous gynaecological diagnosis including endometriosis and polycystic ovarian syndrome. However, Table 2 shows that the majority of women had an uncomplicated medical and gynaecological history. 19.7% of women were current smokers. 16.3% had a history of subfertility, which was significantly more likely in those aged greater than 35 years ($p = .005$).

Investigations performed

94.2% of women ($n=277$) received the full complement of investigations; glycosylated haemoglobin (HbA1c), thyroid function tests, anti-phospholipid antibodies, an autoantibody screen and an inherited thrombophilia screen. Of the remaining 5.8% ($n=17$), the majority of women had four out of five investigations performed and recorded. An autoantibody

Table 2. Maternal characteristics at the time of the second miscarriage.

	Frequency (n)	Percentage (%)
Age		
≤35	190	64.6%
>35	104	35.4%
Smoking		
Current smoker	58	19.7%
Non-smoker	111	37.8%
Unknown	125	42.5%
History of subfertility		
History of subfertility	48	16.3%
No history of subfertility	227	77.2%
Unknown	19	6.5%
Medical history		
Medical history	57	19.4%
No medical history	218	74.2%
Unknown	19	6.5%
Gynaecological history		
Gynaecological history	42	14.3%
No gynaecological history	233	79.3%
Unknown	19	6.5%

screen included testing for anti-nuclear antibodies, extractable nuclear antigen, anti-neutrophil cytoplasmic antibody, rheumatoid factor and others as clinically indicated. A diagnosis of anti-phospholipid syndrome was made in the women with abnormal anti-phospholipid antibodies – lupus anticoagulant, anti-cardiolipin antibodies and anti-B2 glycoprotein-I antibodies – in association with adverse pregnancy outcome and vascular thrombosis. The diagnosis was confirmed by two positive tests three months apart as per the international guidelines (Keeling 2012). Additional investigations arranged included hormonal analysis (20.4%, 60/294), pelvic ultrasound scan (20.1%, 59/294), parental blood karyotyping (19.7%, 58/294) and cytogenetic analysis of products of conception (6.5%, 19/294).

Test results obtained

As demonstrated in Figure 1, the majority (69.4%, $n=204$) of women with a recurrent miscarriage had no causative factor identified. 1.4% of women ($n=4$) had a test result of an uncertain significance. This included three women with an isolated increase in a single autoimmune antibody (anti-smooth muscle antibody, anti-gastroparietal cell antibody) and one woman with an isolated increase in anti-thyroid peroxidase antibodies.

Table 3 shows the prevalence of causative factors identified in this cohort. A positive autoantibody screen was the most frequent abnormality, seen in 15% ($n=44$) of women investigated. Of those with thyroid dysfunction (9.2%, $n=27$), the majority of women were sub-clinically hypothyroid (8.8%, $n=26$). Overt hypothyroidism was seen in one woman (0.3%). Anti-phospholipid syndrome, uterine anatomical anomaly and abnormal foetal cytogenetics had the same rate of occurrence (1%, $n=3$).

Management

All of the women who attended the CUMH Pregnancy Loss Clinic met with Specialist Bereavement midwives and received supportive care. This consisted of emotional and psychological support, supplemented by personal contact and an early pregnancy ultrasound in a subsequent pregnancy. Of those with idiopathic recurrent pregnancy losses,

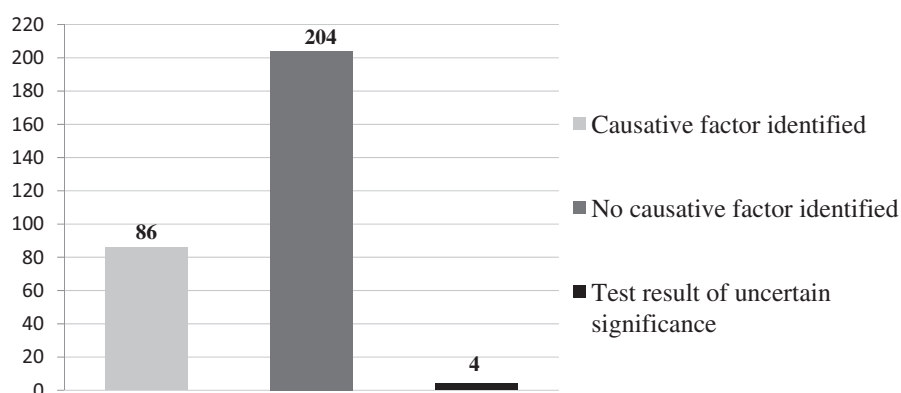


Figure 1. Causative factors identified.

51.3% ($n=102$) received supportive care, alone. Whereas, 56.8% of all women ($n=167$) were prescribed a pharmacological treatment for their next pregnancy.

Table 4 outlines the frequency of use for each medication. Aspirin was the most commonly prescribed drug, used in 45.2% of all women ($n=133$). Indication for its use in a subsequent pregnancy included a positive autoantibody screen. Aspirin was used in combination with LMWH in women with a positive thrombophilia screen or anti-phospholipid syndrome. Lastly, aspirin was prescribed in 38.2% of women ($n=76$) with no causative factor identified following two consecutive losses. Women aged greater than 35 and those with a medical history were significantly more likely to be prescribed medication ($p=.001$, $p=.024$, respectively). The prescription of aspirin was significantly more likely in those aged greater than 35 ($p=.001$), while women with a history of subfertility ($p=.001$) or polycystic

ovarian syndrome ($p=.020$) were more likely to be prescribed progesterone.

Subsequent pregnancy outcome

82.3% of women ($n=242$) achieved a subsequent pregnancy and returned to CUMH for antenatal care. Women aged greater than 35 years and those who were current smokers were significantly less likely to conceive a further pregnancy ($p=.017$, $p=.012$, respectively). The identification of a putative cause for previous miscarriages did not affect the likelihood of conception ($p=1.000$). Of those who did conceive a subsequent pregnancy, 72.7% ($n=176$) had a live birth, while 25.2% of women ($n=61$) experienced a third miscarriage. Three women were found to have an ectopic pregnancy, while one stillbirth and one termination of pregnancy were identified in the cohort (Figure 2).

The influence of maternal characteristics on subsequent pregnancy outcome is detailed in Table 5. The likelihood of achieving a live birth *versus* experiencing a third miscarriage is compared in all women who conceived a subsequent pregnancy and returned to CUMH for antenatal care. Women aged greater than 35 years were significantly more likely to experience a subsequent pregnancy loss ($p=.027$). There was no statistically significant difference ($p=.072$) in the live birth rate between women who had had a cause identified for their previous miscarriages (65.2%, $n=45$) and those who had idiopathic pregnancy losses (76.2%, $n=128$). Women prescribed any medication were more likely to achieve a live birth ($p=.016$). However, the prescription of aspirin ($p=.096$) or progesterone ($p=.069$) alone did not significantly affect pregnancy outcome.

Table 3. Causative factors identified.

	Frequency (n)	Percentage (%)
Abnormal autoantibody screen	44	15.0%
Thyroid dysfunction	27	9.2%
Factor V Leiden mutation	10	3.4%
Polycystic ovarian syndrome	6	2.0%
Prothrombin gene mutation	4	1.4%
Anti-phospholipid syndrome	3	1.0%
Uterine anatomical anomaly	3	1.0%
Abnormal foetal cytogenetics	3	1.0%
Abnormal HbA1c	1	0.3%
Parental balanced translocation	1	0.3%

Table 4. Medical therapies initiated.

	Frequency (n)	Percentage (%)
Aspirin	133	45.2%
Progesterone	47	16.0%
Low molecular weight heparin (LMWH)	20	6.8%
Levothyroxine	13	4.4%
Metformin	7	2.4%
Human chorionic gonadotropin (β HCG)	2	0.7%

Discussion

A total of 294 women attended the CUMH Pregnancy Loss Clinic over a five year period. Following routine

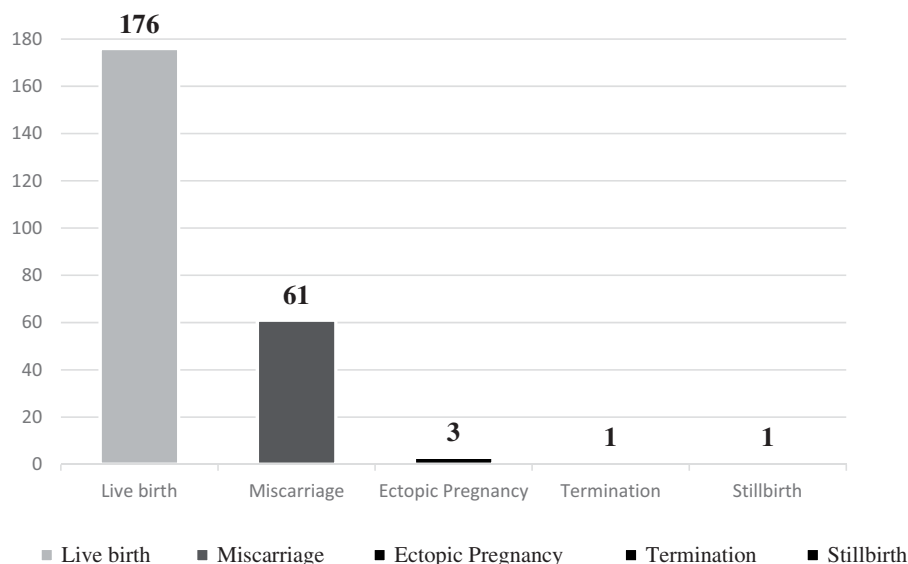


Figure 2. Subsequent pregnancy outcome.

Table 5. Maternal characteristics and outcome of a subsequent pregnancy.

Maternal characteristics	Live birth (n, %)		Miscarriage (n, %)		p Value
Age >35	50	64.9%	27	35.1%	.027
Smoking	26	61.9%	16	38.1%	.156
Subfertility	26	72.2%	10	27.8%	1.000
Medical history	26	60.5%	17	39.5%	.055
Gynaecological history	22	73.3%	8	26.7%	1.000
Putative cause identified for pregnancy losses	45	65.2%	24	34.8%	.072
Abnormal autoantibody screen	19	59.4%	13	40.6%	.089
Thyroid dysfunction	14	58.3%	10	41.7%	.085
Factor V Leiden mutation	7	100.0%	0	0.0%	.194
Prescribed medication	88	67.2%	43	32.8%	.016
Prescribed aspirin	65	66.3%	33	33.7%	.096
Prescribed progesterone	22	59.5%	15	40.5%	.069

investigations, a causative factor was identified in 29.3% of women with two consecutive losses. Medications including aspirin (45.2%), progesterone (16%), LMWH (6.8%), levothyroxine (4.4%) and metformin (2.4%) were prescribed for future pregnancy. A subsequent pregnancy was conceived by 82.3% of women, with 72.7% achieving a live birth.

Current investigation protocols at the CUMH pregnancy loss clinic identified a putative diagnosis in a minority (29.3%) of women. A prevalence of 3.4% for factor V Leiden mutation carriage is similar to the 4% reported by Habayeb and Konje (2004). However, anti-phospholipid syndrome (1%), uterine anatomical anomaly (1%) and parental chromosomal rearrangement (0.3%) were less common than reported in previous studies (Habayeb and Konje 2004; Cohn et al. 2010; Marquard et al. 2010). The lower prevalence in our study can be at least partially attributed to differences in investigation protocols. Women attending the CUMH Pregnancy Loss Clinic with a history of two consecutive miscarriages are not routinely offered pelvic ultrasound scan or parental karyotyping. Consequently, our idiopathic category of 69.4% is higher than that of Marquard et al (2010), but remains within the prevalence of 18–80% reported in the literature (Brigham et al. 1999; Habayeb and Konje 2004).

Autoantibody positivity was the most prevalent abnormality identified. However, the role of investigating for autoantibodies in women with recurrent miscarriage remains uncertain. Some studies have suggested an increased frequency, while others report the opposite (Bustos et al. 2006; Ticconi et al. 2010). We identified a prevalence of 15% which is in line with values of 3–16% seen in healthy individuals (Habayeb and Konje 2004, 2019–02 Ticconi et al.2010; McSweeney et al. 2017). This finding challenges the previously suggested association of autoantibodies with recurrent miscarriage (Ticconi et al. 2010).

The excellent outcome of pregnancy following two consecutive miscarriages has been demonstrated in this study. Overall, 82.3% of women conceived a subsequent pregnancy, with a 72.7% live birth rate. These findings are similar to studies which report that approximately 70% of women with two recurrent losses will conceive a subsequent pregnancy, with a 70% success rate (Clifford et al. 1997; Brigham et al. 1999; Habayeb and Konje 2004). However, increasing maternal age reduces the chance of a successful pregnancy; some authors report a 92% chance of subsequent pregnancy success in a women aged 20 years, compared to just 60% in a

woman aged 45 years with a similar history (Brigham et al. 1999). The impact of maternal age on pregnancy outcome is similarly demonstrated in this present study. Women aged greater than 35 years were not only less likely to conceive a further pregnancy ($p = .017$) but were also significantly more likely to miscarry ($p = .027$). Nonetheless, 64.9% of women aged greater than 35 still achieved a live birth in a subsequent pregnancy.

The lowest live birth rates in this cohort were seen in those with abnormal autoantibodies (59.4%) and thyroid dysfunction (58.3%). However, the difference in pregnancy outcome for women with or without these abnormalities failed to reach statistical significance ($p = .089$ and $p = .085$, respectively). Interestingly, the live birth rate was highest in those with factor V Leiden mutation (100%) although the numbers in this group were small. All the women ($n=7$) with a factor V Leiden mutation were treated with low dose aspirin and LMWH in a subsequent pregnancy. This management appears to have improved the chances of a live birth in this group. However, the numbers in our study are not large enough to make any definitive conclusions with regards to pharmacological treatment.

Women with idiopathic pregnancy losses had a live birth rate of 76.2%, which is consistent with the rates of 70% and 75% reported in the literature (Clifford et al. 1997; Brigham et al. 1999). All of the women attending the CUMH Pregnancy Loss Clinic met with Specialist Bereavement midwives. In those with idiopathic pregnancy losses, 51.3% received supportive care, alone. However, the remainder of women were prescribed a pharmacological treatment in addition. The likelihood of being prescribed medication was influenced by maternal characteristics. Age ($p = .001$) and medical history ($p = .024$) were statistically significant variables. There is increasing evidence that recurrent pregnancy loss is associated with future adverse pregnancy outcome, in particular placental dysfunction disorders. Therefore, this is the most likely reason for prophylactic treatment, such as low dose aspirin being used in these women (Kozer et al. 2003; van Oppenraaij et al. 2009 2019–02Gunnarsdottir et al. 2014; Bartsch et al. 2016).

No statistically significant difference was found in the subsequent pregnancy outcome between women with a causative factor identified *versus* the women with idiopathic pregnancy losses. This was true for both the likelihood of conception ($p = 1.000$), as well as the likelihood of a

subsequent live birth ($p = .072$). Furthermore, although the CUMH Pregnancy Loss Clinic does not routinely offer all women investigations for uterine or endometrial abnormalities, the live birth rate in our cohort was similar to that from other units, including units where such screening is offered (Habayeb and Konje 2004; Marquard et al. 2010). These findings suggest that supportive care alone is probably the single most effective therapy for women with two consecutive losses. Over-investigation and empirical treatment should therefore be avoided, with a greater emphasis placed on psychological support and risk factor modification in this group. Furthermore, investigation protocols must be refined to only search for causes of recurrent miscarriage with evidence-based treatments. Evaluation of supportive care in randomised control trials is needed.

Conclusions

Current management of women with a history of two consecutive miscarriages and no living child at the CUMH Pregnancy Loss Clinic achieves excellent reproductive outcomes. Supportive care and risk factor modification have been suggested as the most effective factors in the management of these women. However, medical investigation is necessary to identify potentially treatable causes of recurrent pregnancy loss. Couples with the most favourable prognostic features have subsequent live-birth rates which are comparable to that of the normal population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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