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ORIGINAL ARTICLE

Pregnancy outcomes following recurrent miscarriage

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Abstract

Background Recurrent miscarriage affects 1–2% of the population, and the literature has focussed on causes, treatment, and live birth rate.

Aim This study aimed to assess the reproductive outcomes for patients who attended a specialist recurrent miscarriage clinic for investigation and treatment.

Methods Prospective analysis of all patients who attended a recurrent miscarriage clinic from January 2014 to January 2021.

Results Of the 488 patients who attended a specialist clinic, 318 had a further pregnancy with 299 included in this study. The median age was 37 years, with 55.6% having a previous live birth. The subsequent live birth rate was 75.3%, 22.0% had a further pregnancy loss, 1.7% had an ongoing pregnancy, and 1% attended another institution after the second trimester. The rate of preeclampsia was 2.2%, pregnancy-induced hypertension was 2.2%, fetal growth restriction was 5.3%, preterm birth ≤ 34 weeks was 1.8%, and preterm birth > 34 weeks < 37 weeks was 6.6%.

Conclusion Patients who attend a dedicated recurrent miscarriage clinic for investigation and treatment have a high live birth rate in a subsequent pregnancy. A subsequent pregnancy following recurrent pregnancy loss does not appear to be associated with an increased risk of adverse pregnancy outcomes.

Keywords Counselling · Infertility · Pregnancy outcomes · Recurrent miscarriage

Introduction

Sporadic miscarriage is common and occurs in approximately 10–20% of pregnancies [1]. Recurrent miscarriage, as defined as three consecutive first-trimester miscarriages, is less common and affects 1–2% of the population [2]. There are approximately 23 million miscarriages worldwide each year, which poses significant physical and psychological consequences [1].

Literature around recurrent pregnancy loss has largely focused on the causes, treatment options, and live birth rate following recurrent miscarriage [3]. However, pregnancy following recurrent miscarriage has been shown to be associated with an increased incidence of adverse pregnancy outcomes such as preterm birth and perinatal death [4]. Risk factors for recurrent miscarriage include maternal age younger than 20 or greater than 35, black ethnicity, smoking, BMI ≤ 18.5 kg/m^2 or BMI ≥ 30 kg/m^2, paternal age greater than 40, previous miscarriages, and air pollution [1]. Investigations which are recommended in patients with recurrent miscarriage include pelvic ultrasound, lupus anticoagulant, anticardiolipin antibodies, beta-2 glycoprotein antibodies, and thyroid function. Chromosomal analysis of pregnancy tissue [5] can also be performed and parental karyotyping undertaken pending the results. There is a need for further studies to examine obstetric and maternal outcomes in subsequent pregnancies following investigation and treatment for recurrent miscarriage.

Current treatment options include supportive care in the form of attendance at an early pregnancy unit. The use of low molecular weight heparin and aspirin is recommended for those diagnosed with antiphospholipid syndrome [2]. The treatment of hypothyroidism with Eltroxin is also recommended.

This study aimed to look at the reproductive outcomes for patients attending the recurrent miscarriage clinic following investigation and who had supportive care.

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Methods

This was a prospective analysis of all women who attended a recurrent miscarriage service in a tertiary maternity hospital from January 2014 to December 2021. Patients were followed until August 2022 to assess subsequent pregnancy outcome if they conceived. Patients were referred to a dedicated consultant-led clinic to undergo investigations and offered treatment for recurrent miscarriage as appropriate. Criteria for referral to our service were three consecutive miscarriages.

Patients were identified when they attended the clinic and all those who attended since 2014 were included. Patient demographics were recorded from the first visit and results from investigations were added when completed. Patient demographics were recorded in terms of age and previous live birth. Investigations included a pelvic ultrasound, thyroid function tests, cytogenetic testing on products of conception, acquired thrombophilia testing, and when indicated parental karyotyping and inherited thrombophilia testing. Data was collected on first and second-trimester losses, live birth, preterm birth, pregnancy interval, preeclampsia, pregnancy-induced hypertension, stillbirth, neonatal death, fetal growth restriction, and attendance at the consultant-led antenatal clinic. The use of aspirin, low molecular weight heparin, and progesterone was recorded. A first-trimester ultrasound was offered to all women who subsequently conceived. Basic descriptive statistics were used to describe on the relevant demographics and obstetric outcomes.

Results

There was a total of 488 women who attended the recurrent miscarriage clinic between 2014 and 2021. Of these, there were 318 patients who attended on a subsequent pregnancy. Data on the subsequent pregnancy was unavailable in 19 of these patients, and they were excluded from further analysis.

Patient characteristics

The median age was 37 years (range 21 to 44 years). Of those who attended the recurrent miscarriage clinic, 53.5% ($n=160$) had a previous live birth, and 45.5% ($n=136$) had no previous live birth; history was unavailable in 3 patients (1.0%). Patients who had no previous live birth are referred to as having a primary recurrent miscarriage, and those with a previous live birth are referred to as having a secondary recurrent miscarriage.

Results of investigations performed

An overview of the investigations performed is shown in Table 1. Cytogenetics on products of conception was performed in 34.8% ($n=104$) and was abnormal in 25.1% ($n=75$). Parental karyotyping was performed in 40.5% ($n=121$), and 1.7% ($n=5$) of couples who had a karyotype performed had an abnormal result. The majority of patients had an ultrasound performed 96.7% ($n=289$), and 21.7% ($n=65$) of these were abnormal. The most common abnormal finding was a fibroid in 10.7% ($n=32$) followed by an endometrial polyp in 3.3% ($n=10$). Other abnormal findings on ultrasound included a uterine septum in 2.0% ($n=6$) patients, and polycystic ovaries were reported in 1.7% ($n=5$) patients. A total of 12.4% ($n=37$) of patients had thyroid dysfunction. Acquired thrombophilia was tested for in 99.7% ($n=298$) patients and was normal in 91.3% ($n=273$); antiphospholipid syndrome was diagnosed in 8.4% ($n=25$) patients. Nine patients were tested for inherited thrombophilia, and the result was negative in all cases.

Table 1 Patient investigation and results for recurrent miscarriage

	n	% of total patients
Total number of patients	299	100
Previous live birth		
Yes	160	53.5
No	136	45.5
Unknown	3	1.0
Cytogenetics performed	104	34.8
Abnormal	75	25.1
Normal	28	9.4
No result	1	0.3
Parental karyotype tested	121	40.5
Abnormal	5	1.7
Normal	116	38.8
Ultrasound performed	289	96.7
Normal	224	74.9
Fibroids	32	10.7
Polycystic ovaries	5	1.7
Polyps	10	3.3
Ovarian Cyst	4	1.3
Septum	6	2.0
Other abnormality	8	2.7
Thyroid function tested	278	93.0
Normal	241	80.6
Abnormal	37	12.4
Acquired thrombophilia tested	298	99.7
Abnormal	25	8.4
Normal	273	91.3
Inherited thrombophilia tested	9	3.0
Abnormal	0	0.0

Pregnancy outcome

There were 299 patients who had a subsequent pregnancy between January 2014 and December 2021, following investigation for recurrent miscarriage and were available for analysis. Table 2 outlines the pregnancy outcomes, obstetric complications, and mode of delivery. Of the 299 patients, 75.3% ($n=225$) went on to have a live birth, and 20.4% ($n=61$) had a first-trimester miscarriage. There were 2 ectopic pregnancies (0.7%), 1 stillbirth (0.3%) and 1 second trimester miscarriage (0.3%). Three patients (1%) were lost to follow-up in a subsequent pregnancy after the first trimester, and 1 (0.3%) patient had a termination of pregnancy. Five patients (1.7%) had an ongoing pregnancy beyond the first trimester at the time of data collection.

Treatment and supportive care

The pregnancy interval between miscarriage and subsequent pregnancy was less than 6 months in 29.4% ($n=88$), 6 to 12 months in 37.1% ($n=111$), and over 12 months in 22.4% ($n=67$) and was undocumented in 11.0% ($n=33$). Patients who attended the recurrent miscarriage clinic were prescribed progesterone supplementation until 16 weeks gestation in 58.2% ($n=174$). There were 14.4% ($n=43$) who were prescribed Eltroxin, 23.7% ($n=71$) were treated with aspirin, and 14.0% ($n=42$) were given low molecular weight heparin. The majority of patients had an early pregnancy scan, 93.0% ($n=278$) and, 73.9% ($n=221$), attended consultant-led antenatal care.

Table 2 Pregnancy outcomes, complications, and mode of delivery

	n	%
Total number of subsequent pregnancies	299	100
Pregnancy outcome		
Livebirth	225	75.3
First-trimester miscarriage	61	20.4
Ectopic	2	0.7
Second trimester miscarriage	1	0.3
Stillbirth	1	0.3
Ongoing pregnancy	5	1.7
Lost to follow-up in second trimester	3	1.0
Termination of pregnancy	1	0.3
Total number of pregnancies > 24 weeks	226	75.6
Pregnancy complication		
Preeclampsia	5	2.2
Pregnancy induced hypertension	5	2.2
Fetal Growth restriction	12	5.3
Preterm delivery ≤ 34 weeks	4	1.8
Preterm delivery > 34 + 1 < 37 + 0	15	6.6
Mode of delivery		
Vaginal delivery	131	58.0
Operative vaginal delivery	9	4.0
Cesarean section	84	37.2
Unavailable	2	0.8

Pregnancy complications

Of the 226 patients who had a live birth or stillbirth, 2.2% ($n=5$) of patients developed preeclampsia, and 2.2% ($n=5$) developed pregnancy-induced hypertension. In total, 5.3% ($n=12$) developed intrauterine growth restriction. There were 1.8% ($n=4$) of patients who delivered at < 34 weeks and 6.6% (n = 15) who delivered between 34 + 0 and 37 + 0 weeks gestation. There was one set of dichorionic twins who were born at 35 weeks of gestation; all other pregnancies were singleton pregnancies. There was one stillbirth and three neonatal deaths.

Mode of delivery

There were 58.0% ($n=131$) who had a vaginal delivery, 4.0% ($n=9$) had an operative vaginal delivery, and 37.2% ($n=84$) had a cesarean section; delivery information was unavailable in 0.8% ($n=2$) of patients.

Discussion

This prospective study aimed to determine future pregnancy outcome for patients who attended a recurrent miscarriage clinic for investigation and treatment. All of this data was collected prospectively with accurate data collection and follow-up. There were some patients who were lost to follow-up in a subsequent pregnancy. Patients attending the clinic were more likely to be experiencing primary recurrent miscarriage than secondary recurrent miscarriage. In this patient cohort, the cause of recurrent miscarriage remained largely unexplained, consistent with large population studies [6]. The most likely abnormal finding during investigation for recurrent miscarriage was abnormal cytogenetics followed by a fibroid on ultrasound. Abnormal cytogenetics on products of conception were noted in 72.1% of patients who had the investigation performed; abnormal cytogenetics are an explanatory finding for a single miscarriage rather than a recurrent miscarriage [5]. There were 0.2% of couples who had an abnormal parental karyotype.

Of the patients who attended the recurrent miscarriage clinic, 170 either did not conceive again during the follow-up period or did not attend our institution for a further pregnancy. We are unable to ascertain whether these patients did actively try to conceive again or whether they decided not to have any further pregnancies. Some patients will not attend the hospital for a miscarriage at an early

gestation, and therefore, the miscarriage rate may be somewhat underestimated.

Subsequent pregnancy outcomes were reassuring with 75.3% of patients having a livebirth and 22.0% a further pregnancy loss. The live birth outcome was in line with international previous studies [7]. The PROMISE trial which investigated the use of progesterone in recurrent miscarriage showed two-thirds of women with recurrent miscarriage will ultimately have a live birth [7].

The incidence of preeclampsia was low at 2.2% as was pregnancy-induced hypertension at 2.2%; larger studies have shown the incidence of preeclampsia in a population to be up to 4.6% [8]. However, given the small sample size, this is not in keeping with larger-scale studies which show adverse obstetric outcomes with a history of recurrent miscarriage. The incidence of fetal growth restriction at 5.3% was also in line with population-based studies [9]. Research has previously linked recurrent miscarriage with an increased risk of preterm birth within a much larger cohort study [4]; however, within this smaller cohort, the rate of preterm birth was in line with population studies [10].

The majority of patients in this study attended consultant-led care for antenatal care as recurrent miscarriage has been associated with adverse pregnancy outcomes. While the data shown is reassuring to patients who conceive again following investigation for recurrent miscarriage, there was a large number of patients who either did not conceive again or did not attend for supportive care. This data provides useful information which can be used for informing patients about the pregnancy outcome of patients who have attended this recurrent miscarriage clinic.

Conclusion

Patients who attend a dedicated recurrent miscarriage clinic for investigation and treatment have a high live birth rate in a subsequent pregnancy.

Author contribution DC, SD, and CA planned the study; NF, AMcE, and SC undertook data collection; NF interpreted the results and drafted the manuscript; and DC, CA, and SC revised the manuscript. All gave final approval.

Declarations

Ethical approval This study attained full ethical approval from the National Maternity Hospital Ethics Committee.

Conflict of interest The authors declare no competing interests.

References

1. Quenby S, Gallos ID, Dhillon-Smith RK et al (2021) Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 397:1658–1667. https://doi.org/10.1016/S0140-6736(21)00682-6
2. Guideline RG-t (2011) The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. RCOG: London, UK
3. Rai R, Regan L (2006) Recurrent miscarriage. Lancet 368:601–611. https://doi.org/10.1016/S0140-6736(06)69204-0
4. Field K, Murphy D (2015) Perinatal outcomes in a subsequent pregnancy among women who have experienced recurrent miscarriage: a retrospective cohort study. Hum Reprod 30:1239–1245
5. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A et al (2021) Recurrent miscarriage: evidence to accelerate action. Lancet 397:1675–1682. https://doi.org/10.1016/S0140-6736(21)00681-4
6. Jaslow CR, Carney JL, Kutteh WH et al (2010) Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril 93:1234–1243. https://doi.org/10.1016/j.fertnstert.2009.01.166
7. Coomarasamy A, Williams H, Truchanowicz E et al (2016) PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. Health Technol Assess 20:1–92. https://doi.org/10.3310/hta20410
8. Yang Y, Le Ray I, Zhu J et al (2021) Preeclampsia prevalence, risk factors, and pregnancy outcomes in Sweden and China. JAMA Netw Open 4:e218401. https://doi.org/10.1001/jamanetworkopen.2021.8401
9. Nardozza LM, Caetano AC, Zamarian AC et al (2017) Fetal growth restriction: current knowledge. Arch Gynecol Obstet 295:1061–1077. https://doi.org/10.1007/s00404-017-4341-9
10. Vogel JP, Chawanpaiboon S, Moller AB et al (2018) The global epidemiology of preterm birth. Best Pract Res Clin Obstet Gynaecol 52:3–12. https://doi.org/10.1016/j.bpobgyn.2018.04.003