Infertility and subsequent recurrent miscarriage: Current state of the literature and future considerations for practice and research [version 1; peer review: awaiting peer review]

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Abstract

Background: Recurrent miscarriage (RM) and infertility are independently associated with adverse pregnancy outcomes, in addition to psychological sequelae. Experiencing pregnancy loss alongside infertility is particularly difficult. International guidance regarding RM is conflicting, and applicability to women with infertility is undetermined. The aim of this study was to: (i) establish if women/couples with a history of infertility are recognised in the literature on the investigation and management of RM, and (ii) determine if the specific needs of women/couples experiencing RM and infertility are ascertained and incorporated into clinical management strategies.

Methods: We examined the wide-ranging literature to ascertain what gaps existed. Studies were retrieved through searches of PubMed and Google Scholar up to 21 January 2021 using appropriate controlled vocabulary and combinations of key words. No language or study design restrictions were applied.

Results: While women/couples experiencing RM after infertility appear in studies evaluating investigations and proposed treatments, high-quality studies are lacking. Furthermore, they are largely excluded from international clinical guidance and qualitative research.

Conclusions: The experiences of women/couples with RM and infertility and their specific care needs within maternity and fertility services are underexplored. It is unclear from current RM guidelines how best to manage and support this complex cohort. Women/couples with infertility and RM are underserved in the literature and in clinical guidance. Further robust studies are warranted to examine pregnancy outcomes, investigations and treatments currently used. Qualitative research is also required to identify their medical and psychological needs to better support this vulnerable group.
Keywords
Infertility, recurrent miscarriage, pregnancy loss, artificial reproductive technology

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Introduction
Infertility
Infertility is defined by the World Health Organization as, “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular protected intercourse”. It is a significant global health issue; however, variances in infertility definitions internationally make calculations of prevalence difficult. Using consistent algorithms and definitions of primary infertility (inability to have any live birth) and secondary infertility (inability to have an additional live birth), 48 million women worldwide were estimated to be infertile in a 2010 global study across 190 countries. In Europe, the European Society of Human Reproduction and Embryology (ESHRE) approximate that 25 million or one in six couples, are infertile. Consequently, the number of pregnancies conceived by Artificial Reproductive Technology (ART) is increasing. In 2015, 849,811 cycles of ART took place in Europe. The reasons for increasing infertility are complex, with Western diet, obesity and environmental toxins attributed to falling sperm counts and reduced ovulation. While male factors exclusively account for 20-30% of infertility cases, they are contributory in up to 50%. Maternal age remains the single most important determinant of fertility. The current average age of first-time mothers in Europe is 29.5 years, and the number of primigravid women aged 40 and over is increasing. Older mothers are more likely to experience complications of pregnancy or pregnancy loss.

Miscarriage and recurrent miscarriage
A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. Miscarriage occurs in approximately 15% of pregnancies, that is 23 million per year. There is increasing recognition that although miscarriage is common, it is associated with subsequent adverse pregnancy outcomes. Recurrent miscarriage (RM) is a more debated definition. Stirrat defined recurrent pregnancy loss (RPL) as the loss of three consecutive pregnancies before viability and this remains the position of the Royal College of Obstetrics and Gynecology and the American Society of Reproductive Medicine (ASRM) today. ESHRE however defines RPL as the loss of any two pregnancies before viability. RM is also stipulated to describe cases where all pregnancy losses have been confirmed as intra-uterine miscarriages. RM and RPL are however, interchangeable within the literature. These broad definitions span a wide range in gestational age and do not confer significance to a second-trimester miscarriage, which has a different etiology to very early pregnancy loss and where the pathology may be more aligned to that of stillbirth. Additionally, the gestation at which a first-trimester miscarriage occurs matters in relation to pathology and outcomes of subsequent pregnancies. Furthermore, this umbrella term of RPL implies a shared mechanism of loss, which may not be the case - even in the same woman. Recommendations regarding investigation and treatment cannot be wholly applicable to such a varied cohort and without clear categorization, discerning any effects of clinical management can be challenging. In this review, primary RM refers to at least two consecutive first-trimester miscarriages (<12 weeks’ gestation), inclusive of biochemical pregnancy, with any variances specified.

RM is calculated to affect 1-3% of the fertile population, with a recent series estimating prevalence to be 0.7% (3 or more) or 2.6% (2 or more), based on definitions used. RM is recognized as a prognostic indicator for subsequent pregnancies and adverse pregnancy outcomes including antepartum hemorrhage, diabetes, preterm birth, small for gestational age and perinatal death. Infertility is also an independent risk factor for adverse pregnancy outcomes, including pre eclampsia, placental abruption, and placenta previa, compared with women in the general population. It is not unreasonable to conclude that a cohort of women experiencing infertility with subsequent RM would be at greater risk of pregnancy complications. Similarly, there are established psychological sequelae following adverse pregnancy outcomes and infertility. There is evidence that enhanced support in subsequent pregnancies following RM is an effective intervention and is welcomed by women, as is counselling of those experiencing infertility.

Recurrent implantation failure
Parallel to those experiencing RM after infertility are women who experience recurrent implantation failure (RIF). RIF is the absence of implantation after repeated embryo transfers. There is no agreed international definition of RIF and a recent Canadian guideline noted 13 variations on the definition. These reflect inconsistencies in the number of failed embryo transfers, the number, stage and quality of embryo(s) transferred, as well as in the definition of implantation. Women who experience RM or RIF following in vitro fertilization (IVF) or other ART for infertility are a cohort bearing a combination of complex losses. Accordingly, they may have similar needs for additional supports in trying to conceive, or in pregnancy.

Given the concerns raised about the guidance for RM, we set out to examine the literature and current clinical guidelines to assess whether the needs of women/couples experiencing infertility and RM were addressed or not, and to identify and gaps. We anticipated that overlaps could exist in the care pathways of those experiencing RIF or RM after infertility, thus we included studies addressing the investigation and management of RIF.

Methods
The objective was to examine the literature regarding RM in women with infertility. Within this, the aim was to establish if women with a history of infertility were recognised in the literature pertaining to the investigation and management of RM. We sought to identify any common aetiology or risk factors for RM and infertility and current research interests. A further purpose was to determine if the specific needs of women (and their partners) experiencing RM and infertility were identified and subsequently incorporated into management or care strategies. These broad aims and the breadth of topics which needed to be explored precluded a systematic review.
Studies examining RM after primary or secondary infertility were included. Studies including RIF were also examined as it is often discussed alongside RM after ART. Published literature was retrieved through searches of PubMed and Google Scholar up to 21 January 2021 using appropriate controlled vocabulary and combinations of key words (recurrent miscarriage, recurrent pregnancy loss, recurrent implantation failure, habitual abortion, infertility, assisted reproduction, assisted reproductive technology, and in vitro fertilization). The search was conducted without a timing restriction, but with prioritization of publications since 2010 to align with current guidelines and the latest research developments. Studies of all designs published in English were reviewed, and additional publications were identified from the bibliographies of these articles.

**Results**

The management of women or couples presenting with either infertility or RM is well described within international guidelines and the pursuit of new treatments is ongoing. In this overview, the common links between RM and infertility will be discussed, including age, aneuploidy, pre-implantation genetic testing (PGT), diminished ovarian reserve, male factors, implantation, as well as the current international guidance and the psychological impacts of these conditions.

**Recurrent miscarriage and infertility**

Although they are largely treated as separate entities, RM and infertility share many common risk factors. In an overview of these reproductive issues, Agenor and Bhattacharya identified maternal age, obesity, smoking, alcohol, medical conditions (specifically diabetes, polycystic ovarian syndrome, endometriosis, thyroid disorders, and cancer treatments such as radiotherapy and chemotherapy) and uterine defects such as polyps, fibroids and septae as being common to both groups. However, after assessment for anatomical and endocrine variabilities, autoimmune disease, thrombophilia (RM cohort), infection (infertility cohort) and contributory male factor, namely abnormal semen parameters which can be affected by paternal age, medical conditions or lifestyle factors, up to 50% of those with RM and 30% of those with infertility will be left without explanation as to why they cannot achieve or maintain pregnancy. This implies that much has yet to be discovered in this area, and reflects the complex process of conception.

**The relationship between miscarriage and infertility**

The literature demonstrates that infertility and miscarriage are likely to co-exist. As far back as the 1950s, an American prospective cohort study demonstrated that women who required at least six months to conceive were more likely to miscarry, with this effect augmented by a history of prior miscarriage and maternal age greater than 35 years. In structured interviews examining obstetric history for miscarriage risk factors in a stratified random sample of Danish women in 1986, delayed time to conception (>1 year) was associated with a higher rate of miscarriage. Many European and American studies examined this link in the 1990s. Two large cohort studies of over 5000 women demonstrated times to conception for first pregnancies which ended in miscarriage were 1.68 and 1.23 times longer respectively than the time to conception of live births. A smaller cohort study found that women diagnosed as having unexplained secondary infertility (n=43) had a three-fold risk of miscarriage and half the expected number of live births compared with the general population. A prospective observational study of 124 women found an increased rate of pregnancy loss in women with infertility compared to controls (70% vs 21%, relative risk (RR) 2.6). In their retrospective cohort study of 3053 women, Whitley et al. found that women with primary or secondary infertility had an approximately fourfold increase in risk of fetal death (stillbirth or miscarriage) compared with women who reported no fertility issues (odds ratio (OR): 3.92; 95% confidence interval (CI): (3.02, 5.07)). Gray and Yu Wu determined that miscarriage rates were higher in pregnancies preceded by infertility in a cohort of 1572 women (23% vs 14%, adjusted OR (aOR)= 1.71, 95% CI = 1.26-2.94). A case-control study from 2007 showed that women who took over 12 months to conceive were twice as likely to miscarry (aOR 2.01, CI 1.42-2.84). Women with a known fertility issue were also at greater risk of miscarriage, with those experiencing tubal causes having the highest odds, even after adjustment for fertility treatment (aOR 2.28, CI 1.24-4.20). The relationship between RM and infertility is illustrated less frequently in the literature. In 1991, Cauchi et al. in a small (n=165) double-blinded randomized control trial of white cell immunization in women with RM, identified that higher order miscarriage (> 5), longer miscarriage history, increased intervals between conceptions and delayed or assisted conception, were associated with further subsequent miscarriage. Likewise, in 1994 Clifford et al. in a cohort of 500 with RM, 32% reported delayed time to conception (>12 months) and 23% received fertility treatment. More recently in 2016, Kling et al. endorsed this link between RM and infertility, demonstrating in an observational study (n=228) that couples with RM aged 35-39, who have had sub-fertility for over 3 years, with more than 3 miscarriages are less likely to conceive and have a live birth, with 17.9% (n=10) of those ages 35-39 developing secondary infertility.

This trend towards secondary infertility following miscarriage is demonstrated in other studies. The self-reported questionnaire data of 2983 women trying to conceive demonstrated a prolonged time to pregnancy following a miscarriage (OR=2.1, (1.4-3.0) p<0.001). A prospective study of 70 women also demonstrated an increased time to conceive after miscarriage and decreased fecundability (OR 0.42, 95% CI 0.28-0.65). A separate prospective cohort also showed a 35% decreased fecundability in women after two miscarriages, however numbers were small (n=23) and the decrease appeared to improve over 12 months. These studies suggest that women with RM who have preceding infertility or delayed conception have lower live birth rates and are at a greater risk of further miscarriage and secondary infertility. These studies are not homogenous,
varying sample sizes and populations, as well as definitions for RM and infertility, and so are not directly comparable. Several studies are over 25 years old. Furthermore, some are retrospective and self-reported, increasing the risk of recall bias. Nonetheless, a definite trend is seen; RM following infertility is poor prognostic indicator for future live birth. Overlapping factors such as maternal age, aneuploidy, diminished ovarian reserve (DOR), male factors and implantation may offer insights and are reviewed below.

Other associations between RM and infertility

**Maternal age.** The dominant common link to both RM and infertility is maternal age. It is well established that there is a gradual decline in female fertility, with the effects most pronounced after the age of 35. This is due to a combination of a reduction in the number of oocytes and a deterioration in oocyte quality. Studies using population registers of pregnant women in Denmark and Norway have demonstrated in very large cohorts that advanced maternal age is strongly associated with lower birth rates, maternal and fetal morbidity as well as miscarriage. Age alone has an independent negative effect on fecundity. It is also evident that age is a greater predictor of pregnancy success than other markers of fertility such as follicle-stimulating hormone (FSH). The risk of miscarriage in women aged 45 years and older is approximately 65%.[5,6] A consistent higher miscarriage rate and lower pregnancy and live birth rate is seen in older women, even in cases with IVF and oocyte donation.[6,7] This trend is commonly observed across all European countries, despite advancements in IVF techniques. Although age is an important prognostic indicator for future pregnancy, there are significant associations for younger women with RM and infertility which will be outlined below.

**Aneuploidy.** Aneuploidy is a definitive cause of pregnancy loss that is strongly associated with age.[8] Aneuploidy is any chromosomal condition that arises from having an additional (trisomy) or missing chromosome (monosomy). Aneuploidy is associated with pregnancy loss in RM and women with infertility. In RM, cytogenetic analysis of pregnancy tissue demonstrated aneuploidy and a cause for miscarriage in 80% of cases in women over 35.[9] Similarly, in an IVF population who had a sporadic miscarriage and subsequent cytogenetic testing, the rate of aneuploidy was 63% in those under 38 years and 80% in those older.[10] In other examinations of pregnancy tissue in RM cohorts however, the rate of aneuploidy in subsequent miscarriages appeared to be lower in women with more than two miscarriages than in those women experiencing sporadic miscarriage, and appeared to decrease further with successive miscarriages.[11-13] This trend was more evident in women under 35 with RM; older women regardless of RM history in these cohorts still demonstrated higher rates of aneuploidy.[14,15]

Cytogenetic testing only partially reveals the potential role of aneuploidy in miscarriage as many pregnancy losses are sub-clinical or occur at the implantation stage.[16] PGT has also demonstrated an increase in aneuploidy with maternal age, even in those embryos that appeared developmentally and morphologically appropriate.[17] Pre-implantation and sub-clinical pregnancy losses were suggested as explanations for unexplained infertility, that is, women were experiencing very early pregnancy losses, rather than failing to conceive.[18] This was refuted in a study of urinary hCG levels in 120 women prior to menstruation, which detected just one implantation in the infertile group against 30 in the control group.[19]

Aneuploidy can therefore explain a significant proportion of miscarriage in those over 35. More studies are required in younger women with RM and infertility to better understand the role of aneuploidy in their pregnancy losses. PGT offers an insight into the early embryo and a possible route to pregnancy for those with a history of aneuploid pregnancy.

**Pre-implantation genetic testing.** PGT is the process of screening cells from embryos for genetic diseases or chromosomal disorders prior to transfer during IVF. A recent review of the evolution of PGT over the last two decades discussed the change in genetic analysis and embryonic biopsy and applicability to couples with RM.[20] Using earlier PGT, Rubio et al.[21] demonstrated the percentage of abnormal embryos was significantly increased in women with RM compared with controls (70.7 vs. 45.1%, p < 0.0001), and that aneuploidy was significantly increased in younger women with RM (P < 0.0001) than in women ≥ 37 years (P = 0.046). A systematic review of studies using early PGT techniques demonstrates miscarriage rates were lower after PGT than natural conception (9% vs 28%).[22] A recent study compared the aneuploidy rate in women with idiopathic RM (≥ 2 miscarriages) undergoing PGT for aneuploidy (PGT-A) to a control group without a history of RM undergoing PGT for monogenic defects (PGT-M).[23] A higher rate of aneuploidy was observed in the RM group compared to the control group (57.4% vs 42% P < 0.001), with a significant difference (48.9% vs 36.9%, P < 0.001) observed in those under 35 years.[24] A higher rate of miscarriage in the younger RM group despite euploid transfer was also seen (26% vs 3% p < 0.03).[25] Shahine and colleagues noted women with RM with diminished ovarian reserve had a higher percentage of aneuploid blastocysts (57% vs 48%, p = 0.03) and a higher incidence of no euploid embryos to transfer (25% vs 13%, p = 0.02), with a significantly higher rate of aneuploidy in those ≤ 38 years (67% vs 53%, p = 0.04).[26] A large study of 3,378 IVF cycles demonstrated an increased rate of aneuploidy among patients with RPL (not defined) (OR 1.330, P < 0.001), prior aneuploid pregnancy (OR 1.439, P < 0.001), or previous failed IVF cycles (OR 1.356, p = 0.0012) compared to fertile controls, even when adjusted for age.[27] In an examination of PGT-A outcomes in women with RIF, RPL (stratified into late and early miscarriage) and other adverse pregnancy outcomes, women with higher order RIF (≥ 5) had increased aneuploidy compared to controls (48.8% vs 33%, p = 0.02), as did those with ≥ 4 early miscarriages (41% vs 33%, p = 0.03).[28] Compared to controls, the miscarriage rate in the RM cohort was higher...
(6.58% vs. 31.11%, p < 0.001, OR = 6.49) and the live birth rate was lower even after euploid transfer (53.49% vs. 34.18%, p = 0.007, OR = 0.56).

These studies suggest that PGT-A detects significant levels of aneuploidy in RM and RIF cohorts and the transfer of euploid embryos does not diminish the risk of implantation failure or miscarriage. This is in keeping with the chromosomal analysis of pregnancy tissue in RM cohorts; younger women with RM are more likely to miscarry euploid embryos83-85. Recent guidelines and reviews on the topic still do not recommend the use of PGT-A in RM cohorts. A recent review of PGT-A, which was not focused on RM cohorts, highlights that the reduction in miscarriage rates is offset against the loss of potentially viable embryos due to false positives86. Kirshenbaum and Orvieto echoed these concerns and called into focus the high false positive and false negative rates of the technique and questioned the methodology and interpretation of recent RCTs, and indeed the dissimance between the technique and the biology of the pre-implanted human embryo87. The most recently published guideline on PGT-A reviewed just two studies focused on RM cohorts, (Murugappan et al. and Shahine et al.), and had no clear guidance for PGT-A in RM88. Murugappan et al. in particular highlight the cost, with a 91% live-birth rate required for PGT-A to become cost effective for couples experiencing RM compared to expectant management89. Greco et al. conclude that IVF/PGT-A is a very expensive way to reduce miscarriage, without increasing the chance of achieving a live birth, and indeed, “given the uncertainty about self-correction, false positive PGT-A results, and/or accuracy of a mosaic diagnosis, there is concern that one may be discarding embryos that may have resulted in healthy babies”90,91,70. Further high quality studies are necessary prior to recommending IVF or PGT in RM cohorts, particularly in younger women. Those with infertility requiring ART and subsequently experiencing RM also need greater analysis to determine the role of aneuploidy and any possible role for PGT.

**Tests of ovarian reserve.** Given the associations with age and aneuploidy, it is reasonable to consider egg quality and ovarian reserve as contributory factors in RM and infertility. Diminished ovarian reserve (DOR) refers to a reduced ovarian follicle count that is measured by FSH level, Anti-Müllerian Hormone (AMH) level or by ultrasound of the antral follicle count92. It is hypothesised that women with low ovarian follicle counts also have reduced oocyte quality. These oocytes are at greater risk of abnormal development, including meiotic non-disjunction and subsequent aneuploidy, resulting in failed implantation or miscarriage93. Women who have had an aneuploid pregnancy have so far not been proven to have statistically significant DOR or earlier menopause, that is aneuploidy is not predictive of premature ovarian failure94-96.

As mentioned above, Shahine et al. noted in a RM cohort (n=102) that aneuploidy rates were highest in women with DOR defined by AMH level <1ng/ml or FSH >10IU/ml on day three97. Women with spontaneous conceptions with severe DOR (n=26, AMH <0.4ng/ml) were found to miscarry at twice the rate as those with AMH ≥1ng/ml (hazard ratio, 2.3; 95% CI, 1.3, 4.3), even with adjustment for age, race, history of RM and obesity98. RM was associated with a low AMH (p=0.04), but just six women had RM99. A systematic review included 15 studies (n=3,082 women) and showed that women with RPL (included losses <20 weeks) were more likely to have DOR, defined by low AMH levels, compared with women who did not have RPL. (OR) 2.77; 95% confidence interval [CI], 1.41–5.46) and low antral follicle count (OR 2.45; 95% CI, 1.16–5.19)77. Women with unexplained RPL also seemed to have a higher association with DOR compared with women whose RPL had a known etiology, as measured by low AMH levels (OR 3.23; 95% CI, 1.81–5.76)77. Wald et al. also noted DOR rates were higher in the unexplained RPL (two losses <20 weeks) cohort (n=177), compared to patients with an identified cause for RPL (n=87) (48% vs 29%, p =0.05), and the DOR rate was increased in those under 38 years old with RPL (22% vs. 12%, p =0.04)79. Notably, these studies did not include chromosomal analysis of pregnancy tissue in investigations for RM and thus DOR and previous aneuploidy could not be correlated.

Abnormal AMH results can also signpost to other disorders associated with RM and infertility. Low AMH levels are also associated with endometriosis, a disorder of ectopic endometrial tissue99. Infertility affects 11.6% of women with diagnosed endometriosis100. Endometriosis is also implicated in RM and RIF99,100. AMH is not however a definitive diagnostic test for endometriosis. Conversely, higher levels of AMH (>10ng/ml), are associated with polycystic ovarian syndrome (PCOS)101. Diagnostic hallmarks of PCOS include oligo or anovulation, hyperandrogenism, and antral follicular excess on ultrasound102. It is thus associated with anovulatory infertility and RM. Higher AMH levels in women with PCOS appear to be associated with poorer ART outcomes103. However, PCOS can be diagnosed by clinical history and ultrasound, and thus the role of AMH in women with PCOS in addition to RM and infertility has yet to be determined.

Overall, ovarian reserve testing in women with RM and infertility does not appear to generate a clear management strategy. The conclusion of the above studies is that a low AMH result would facilitate counselling regarding the prospects of spontaneous conception72,86,87, and may direct care towards PGT or oocyte donation77. Ovarian reserve testing merits RCTs in more defined cohorts of women with infertility and RM if it is to have such a pivotal role in ART counselling96,77.

**Male fertility.** Male factors are an important yet often overlooked link between RM, infertility and aneuploidy. After three miscarriages, most guidelines recommend parental karyotyping16,48. While balanced translocations are found more frequently in RM populations, they are still uncommon overall, and a small proportion are attributable to the male partner90. Globally, male fertility rates are in significant decline49. Further, advanced paternal age (APA) (<40 years) appears to be a more common and significant risk factor for
infertility and RM than previously thought\textsuperscript{12,91}. APA is a suggested contributor to sperm DNA fragmentation and aneuploidy\textsuperscript{92}. Sperm DNA fragmentation is the “separation or breakage of DNA strands into pieces”\textsuperscript{89}. Several case-control studies have now associated sperm aneuploidy with RPL\textsuperscript{92–96}, and that aneuploidy was higher in those men with a RM history, even with a normal sperm count and morphology\textsuperscript{92}. Conversely, Coughlan et al. found variances in sperm DNA fragmentation testing parameters and no clear evidence of an association with RM or RIF\textsuperscript{97}. The clinical significance of sperm aneuploidy, and subsequent management, is uncertain\textsuperscript{98}. Advanced sperm selection techniques are often paired with intra-cytoplasmic sperm injection to ensure structurally intact and mature sperm with high DNA integrity are chosen for fertilisation\textsuperscript{99}. A Cochrane review found that there was insufficient high-quality evidence for sperm selection techniques in RM cohorts to improve live birth rates or reduce miscarriage rates, as did other reviews\textsuperscript{98–101}. The Society for Translational Medicine clinical practice guidelines suggest sperm DNA fragmentation testing should be done for cases of unexplained fertility, failed IUI and in RM\textsuperscript{102}. After initially advising that testing for spermolploidy or DNA fragmentation should not be done in RPL\textsuperscript{103}, the ASRM conceded that sperm aneuploidy testing may be of some benefit in RM or recurrent IVF failure, but needed further study\textsuperscript{104}. In cases of RM and infertility, the male contribution merits greater consideration, as unlike the oocyte, factors affecting sperm quality such as alcohol, smoking and presence of a varicocele are modifiable\textsuperscript{89}. The role of sperm studies beyond semen analysis in RM and infertility and their clinical application remains unknown.

**Implantation Processes.** Cytogenetics and PGT have demonstrated that women with infertility may still experience RM even in the absence of aneuploidy. The processes of fertilization and implantation are complex, and a number of reviews have attempted to shed light on the multiple systems which work collectively for successful implantation to occur\textsuperscript{98,104–106}. The endometrium has an active role in receptivity, signaling and cell recruitment\textsuperscript{109,110}. This is influenced by the health or genetic make-up of the embryo, which signals to the endometrial decidual cells, permitting or rejecting implantation\textsuperscript{110}. A current theory is that disruption of these signaling processes allows aneuploid embryos to implant in a “highly receptive” decidualized endometrium, resulting in “superfertility” and consequently, RM\textsuperscript{109,111}. However, this process appears to be associated with short times to conception (<3 months) and is thus less likely in infertile cohorts, but superfertility rates of 32% have been found in the RM population\textsuperscript{112,113}. Conversely, a “highly selective” endometrium results in delayed conception or recurrent implantation failure\textsuperscript{109}.

The identification of the cellular and molecular mechanisms involved in endometrial receptivity and decidualization is ongoing in a search for clinically applicable therapies. Natural killer (NK) cells have been of particular interest, and while they play a role in pregnancy maintenance, their relationship with cell receptors, cytokines and hormones, and their role

in infertility and RM remains unclear\textsuperscript{108,114,115}. Endometrial biopsy or “scratch” prior to implantation of an embryo has been purported to increase implantation rates, particularly in the RIF cohort\textsuperscript{116}. The biopsy allows for examination to diagnose chronic endometritis and quantification of uterine natural killer cells, but the resulting endometrial injury is also proposed to increase growth factor and cytokines which improve endometrial receptivity\textsuperscript{116}. In a recent review, Günther et al. point to two large reviews in RIF populations, one meta-analysis (n=2062)\textsuperscript{117} and a Cochrane review (n=1063 (intervention), n=1065 (controls))\textsuperscript{118}, which showed an increase in pregnancy rates following endometrial “scratch”\textsuperscript{119}. However, a recent robust RCT with 1063 patients in each arm, demonstrated no difference in birth rates (adjusted OR, 1.00; 95% confidence interval, 0.78 to 1.27) and sub-group analysis showed no benefit to women with RIF (estimated interaction OR, 0.63; 95% CI, 0.35 to 1.15; P = 0.14)\textsuperscript{120}. Considering the evidence quality of the preceding reviews, Günther et al. concluded that endometrial “scratch” should no longer be offered\textsuperscript{119}. There are no published results of RCTs in RM cohorts, and the results of the Scratch in Miscarriage trial are awaited\textsuperscript{121}.

Endometrial biopsy in women with endometriosis has produced some potential insights into RM and infertility. Endometriosis is known to cause structural and functional abnormalities to the hypothalamic-pituitary-ovarian-endometrial axis and thus affects conception, endometrial receptivity and may contribute to embryonal loss\textsuperscript{89,92}. Additionally, endometriosis can take four to 11 years to diagnose\textsuperscript{122}. Freitag et al. demonstrated that women with RIF and endometriosis (n=67) were 1.3 times more likely to have chronic endometritis compared to controls without endometriosis, as demonstrated by raised plasma cell counts on endometrial biopsy\textsuperscript{123}. This is potentially amenable to doxycycline therapy and merits further study to determine the impact on pregnancy rates and outcomes. Fox et al. (2019) performed endometrial biopsies in women with RM (n=29) or unexplained infertility (n=53) and examined the levels of a postulated marker for endometriosis, nuclear protein B-Cell CLL/lymphoma 6 (BCL6), in endometrial samples\textsuperscript{124}. A subset of cases with abnormal BCL6 went to laparoscopy, and endometriosis was found in 9 out of 11 cases of RM and in 20 out of 21 cases of unexplained infertility\textsuperscript{124}. While endometrial biopsy may direct further research in the context of endometriosis, these small studies are insufficient to support routine use in women with RM and infertility.

Immunotherapy has also been a focus of research in these cohorts. Recent systematic reviews have sought to establish if any immunotherapies have made a significant impact on live birth rates, pregnancy rates or miscarriage rates in RM cohorts\textsuperscript{125–128} and RIF cohorts\textsuperscript{129,130}, as have a number of literature reviews\textsuperscript{131–135}. While Achilli et al. looked at women undergoing IVF with and without RM, no specific work has been done in infertility cohorts experiencing RM. A review of five studies demonstrated intravenous immunoglobulin (IVIG) increased live birth rates and pregnancy rates in RIF
populations, but did not find a significant difference in miscarriage rates. Christiansen et al. performed sub-analyses on 13 RCTs in which meta-analyses had shown no benefit to IVIG in RM populations and found some increase in live birth rates in RM populations who received IVIG (RR 1.17, 95% CI 0.95-1.44, p=0.14). A more focused review of women with RM and abnormal NK cell activity/levels found potential benefit in offering immunotherapy to such women but this covered just seven studies and one RCT (intravenous immunoglobulin (IVIG) (four studies), prednisolone, etanercept and intralipid (one study each)). These reviews concluded that there is a paucity of well-designed and adequately powered RCTs in this area and that significant further research is required in order to make clear recommendations. Furthermore, there is no consensus on the function of NK cells (peripheral or uterine), how best to measure cell levels or activity, what immunotherapy is most appropriate, and if these therapies are safe to use in a pregnant population.

These costly investigations and therapies merit rigorous examination in RCTs prior to recommendation. Genes have been identified related to implantation and immune pathways in RPL and fertility cohorts which may better direct biomolecular research and identify future genetic or immune therapies.

**International Guidelines Related to Recurrent Miscarriage.** Current guidelines in RM and related conditions such as thrombophilia and thyroid disease do not provide substantial guidance with regards to investigation or treatment of women with infertility and RM. In their 2017 guideline, ESHRE mention that a history of infertility should have a bearing on investigations, and reference the works of Cauchi et al. in acknowledging that delayed time to conception in RM can affect pregnancy prognosis; however, they do not make any specific recommendations for care of this cohort. Four RM guidelines make reference to IVF treatment but in the context of PGT-A or sperm DNA fragmentation studies, which the guidelines do not currently recommend. American Thyroid Association guidelines on thyroid disease recommend that thyroid stimulating hormone is measured in women with infertility or RM, and that thyroid peroxidase antibodies should be measured in women with RM and/or infertility. Wall et al. provide guidance on imaging in this cohort. The remainder of guidelines on RPL do not discuss infertility in this cohort. A recent publication highlighted how national clinical guidance was inconsistently applied by clinicians in RPL clinics during investigation and treatment of women with RM, but did not discuss the management of women with infertility and RM. A recent Lancet Series on miscarriage found that despite ample clinical guidance, “clinical practice is inconsistent and poorly organised.” A graded care plan for women with sporadic and recurrent miscarriage was suggested, focused on evidence-based investigations and treatments, with additional supportive care. While this Series brings much-needed attention to early pregnancy care and the needs of those experiencing miscarriage, RM after infertility was not addressed. Thus, in the absence of high-quality evidence and robust clinical guidance, the management of this cohort requires greater scrutiny and directed research efforts.

**Psychological Impact of Recurrent Miscarriage and Infertility.** The majority of guidelines acknowledge the psychological needs of the RM population. However, there is no mention of the additional psychological needs of those with infertility or who are undergoing ART. The wider literature, while it addresses the psychological impacts of infertility and RM, treats them as discrete entities. Women with RM are at increased risk of high stress and moderate to severe depression. Research also demonstrates that they would like increased support, as well as awareness of the psychological impact of their experiences, and the recognition from medical staff of an individual life event. Infertility is also associated with depression and anxiety, with stresses exacerbated by financial concerns. It would follow that women experiencing infertility and subsequent RM would be at high risk of psychological morbidity. The sole qualitative study of women experiencing miscarriage after infertility identified that they feel “profoundly alone, and grieve intensely.” Additionally, these women feel responsible for the loss, face significant financial burdens and find it difficult to hope that they will ever become pregnant again. RM and infertility also impact on male partners, however current care models can place men in secondary roles with limited opportunities to articulate their loss and grief. The specific needs of those men and women in their fertility and antenatal care are largely unidentified and likely unmet by current clinical guidance.

**Discussion**

We sought to examine the literature regarding RM in women and couples with infertility, and to identify gaps which could be addressed in future research. It is evident that this cohort are not recognized in the literature and international clinical guidance. We found that women with infertility feature within RM cohorts but are not highlighted as a distinct group. The literature suggests that women experiencing RM with a history of infertility would be at increased risk of further miscarriage and secondary infertility, in addition to lower live birth rates, but more studies are needed to examine pregnancy outcomes in detail. Aneuploidy plays a significant role in RM in women over 35. However, declining aneuploidy rates in successive miscarriages in younger women with RM and infertility deserves greater scrutiny. Further, persistent higher aneuploidy rates compared to controls, but lower successful euploid transfer, indicates more high-quality studies are required to determine any role for PGT or DOR testing in those under 35. In addition, the mechanisms behind successful implantation are not fully understood and larger high-quality RCTs are required to determine the benefits of investigations and immunotherapies. The male contribution to RM and infertility is likely underestimated and potentially improved by lifestyle modification; thus meriting greater consideration and investigation. Furthermore, the lived experiences of women and their partners following RM and infertility and their subsequent needs are sparsely documented.
and are deserving of attention. The international guidelines on RM reflect the lack of high-quality studies and qualitative research and thus fail to consider women and couples with concomitant infertility in recommendations for investigation, treatment and supports in future pregnancy.

Our study has several strengths. This examination of the literature has not been previously conducted to date. It identifies important gaps in the care of women with RM and infertility and their under-representation as a distinct cohort in research. Limitations must also be noted. While all English language study types were included, we did not formally assess the quality of studies. Further, we aimed to identify the overlapping issues between RM and infertility, not the particular conditions, investigations or managements linked to each individual topic. The broad definition of RPL prevents proper stratification and comparison of different types of pregnancy loss, which could advance knowledge in this area. This study has nonetheless (attempted to) established the current state of knowledge and future research areas.

This research identifies a distinct gap in the literature. Women with infertility and subsequent RM are not adequately considered. This may be due to several potential reasons, including a lack of identification of women experiencing RM in infertility cohorts, or a focus on spontaneous conceptions within RM cohorts. These cohorts are also compromised by women without fertility problems undergoing IVF as a treatment for RM\(^\text{[9]}\), a decision which in itself merits further exploration as to whether this is driven by clinicians or women seeking these services.

**Conclusions**

In conclusion, this examination of the literature shows that women and men experiencing infertility and RM are not well represented. Although there is significant overlap between infertility and miscarriage, including but not exclusive to; advanced maternal age, aneuploidy, DOR, PCOS, endometriosis, there is no clear unifying etiology. Rather, this is a complex cohort of women where - in addition to co-morbidities and parallel pathologies - they are grieving the loss of wanted pregnancies and, with trepidation, are contemplating future pregnancy and associated medical treatments. It is unclear from current RM guidelines how best to manage this cohort. The focus of research appears to be on costly investigations, ART and immunotherapy, which are not based on strong evidence. There is limited research on pregnancy outcomes, with a concentration on rates of implantation and live births. Further studies are warranted in women and men with infertility and RM to examine pregnancy outcomes, to review investigations and treatments currently used, and qualitative research is required to identify their medical and psychological needs. Such findings can initiate better supports for this vulnerable group which are currently underserved by the published literature and in clinical guidance.

**Data availability**

No data are associated with this article.

### References


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