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REVIEW ARTICLE

Modern management of recurrent miscarriage

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Recurrent miscarriage (RM), also known as recurrent pregnancy loss, is a distressing condition affecting around 1% of couples trying to conceive It can be very frustrating for both clinicians and patients as, despite intensive workup, no clear underlying pathology is forthcoming in at least 50% of couples. This leads to despair for patients and leaves clinicians at a loss for how to help. Desperation in both camps can promote the uptake of investigations and interventions of unproven benefit. The pathophysiology underpinning RM is incredibly diverse, involving areas such as haematology, endocrinology, immunology and genetics. During the seven to eight years since the UK Royal College of Obstetricians and Gynaecologists published guidelines on this topic in 2011, new evidence and guidance from expert authorities have emerged. Here, these important advances in this challenging field of clinical practice will be reviewed.

KEYWORDS

antiphopholipid syndrome, chromosomal translocation, progesterone, recurrent miscarriage, uterine septum

DEFINITION OF RECURRENT MISCARRIAGE

Recurrent miscarriage (RM) affects around 1% of couples in at least 50% of whom, no obvious pathology can be identified.[1-5] There is a lack of consensus regarding the number of miscarriages required for defining recurrent miscarriage. If the threshold number of miscarriages required for making the diagnosis of RM is set too low, many women who have an otherwise good prognosis would be subjected to unnecessary investigations, whereas setting it too high risks avoidable pregnancy losses in patients with rectifiable pathology. This also has implications for research since inclusion of large numbers of low-risk women with inherently good prognosis would make it difficult to discern any potential benefits of a given intervention for those with underlying pathology. Setting the threshold depends on the background risk for miscarriage, and as discussed later, this risk is closely correlated with female age. Another consideration is whether biochemical or only clinically recognised pregnancies are included since the background risk of losing three clinical pregnancies is low compared to losing three biochemical pregnancies (0.3% vs 22%).[6]

The UK Royal College of Obstetricians and Gynaecologists (RCOG) define RM as 'the loss of three or more consecutive pregnancies'.[5] Because the RCOG considers pregnancy to extend from conception to 24 weeks of gestation, their definition includes biochemical pregnancies. The German, Austrian and Swiss Societies of Gynecology and Obstetrics (DGGG/OEGGG/SGGG) also consider RM as ≥3 consecutive losses.[7] The American Society for Reproductive Medicine (ASRM), on the other hand, defines RM as 'two or more failed clinical pregnancies' (pregnancy in this case requiring ultrasound or histological confirmation) thereby excluding biochemical pregnancies but requiring only two losses.[8] This rationale is supported by a large study involving over 1000 women, which found that the likelihood of detecting an abnormality after two losses was similar to that after three or four or more losses.[2]

FEMALE AGE AND EMBRYONIC ANEUPLOIDY

Spontaneous miscarriage occurs in 10–15% of clinically recognised pregnancies,[6,9] the major underlying cause being

TABLE 1 Background rate of spontaneous miscarriage in relation to female age

Age group (years)	Spontaneous miscarriage (%)
20–24	11
25–29	12
30–34	15
35–39	25
40–44	51

From Nybo Andersen *et al.*[9]

embryonic aneuploidy. Since meiotic chromosome segregation errors in oocytes account for the majority of embryonic aneuploidies and increase with age,[10] the risk of having a miscarriage is strongly influenced by female age (Table 1).[9] Consequently, the background risk of having three miscarriages for women <25 years is around 0.13% but 100 times more likely (~13%) if over 40.[6] Given the impact of female age on embryonic aneuploidy,[10] the rate-limiting risk factor for miscarriage in older women is largely untreatable.

Around 40% of miscarriages in RM patients are chromosomally abnormal,[11] highlighting the importance of embryonic aneuploidy in this population. Hence, most cases that are unexplained from a parental perspective can in fact be explained by embryonic chromosomal abnormalities.[12] Collectively, combined parental and embryonic factors provide an explanation in >90% of RM patients.[12] However, it should be noted that embryonic aneuploidy does not negate the possibility of co-existing pathology in the couple, which occurs in around a quarter of cases.[12]

Karyotyping of subsequent miscarriages using whole genome approaches is therefore informative. Significantly, the likelihood of there being a parental cause is heavily influenced by whether embryonic aneuploidy is present – 85% of patients with euploid miscarriage tissue were found to have an abnormality following RM workup in one study.[12]

Given the contribution of embryonic aneuploidy, it might be expected that screening out aneuploid embryos using in vitro fertilisation (IVF) in combination with preimplantation genetic testing (PGT; note that PGT is the new nomenclature for genetic embryo testing during IVF[13]) would improve outcomes in unexplained RM. However, at present there are a lack of randomised controlled trials (RCTs) investigating whether PGT for aneuploidy screening (PGT-A) is superior to expectant management in RM patients. Recent retrospective data suggest that PGT-A does not increase live birth rates or shorten times to pregnancy in this population.[14] The recently published ESTEEM trial (ESHRE Study into the Evaluation of oocyte Euploidy by Microarray analysis) that evaluated polar body PGT-A for advanced maternal age excluded RM patients but found a reduction in miscarriage rates in the PGT-A arm.[15] On the other hand, another RCT of PGT-A, this time in young good-prognosis patients and involving the much more commonly used blastocyst biopsy approach, did not report a significant reduction in miscarriage rates.[16] For the present, and consistent with a recent ASRM evaluation,[17] there is a lack of robust evidence that PGT-A in patients without known structural chromosomal abnormalities increases the chances of live births or reduces the numbers of miscarriages *en route* to successful livebirth in the RM population.

TABLE 2 Prevalence of abnormal results in recurrent miscarriage patients with ≥3 consecutive pregnancy losses

Abnormality	*n*	%
Parental chromosomal abnormality	492	5.5
Uterine structural defects	506	17.6
Lupus anticoagulant	523	2.5
Anticardiolipin antibodies	537	14.7

From Jaslow *et al.*[2]

ANTIPHOSPHOLIPID SYNDROME (APS)

Antiphospholipid syndrome is found in 5–20% of women with RM (Table 2)[8,18] and is considered the most important treatable cause.[5] Diagnosis of APS requires two components, adverse pregnancy outcome and antiphospholipid antibodies (lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-β2-glycoprotein-I antibodies). Antiphospholipid antibodies are thought to impair pregnancy through various mechanisms, including inhibition of trophoblast function, thrombosis of the utero-placental vasculature and initiation of a local inflammatory response at the maternal-fetal interface.[5,8] Diagnosing APS requires moderate to high titres of aCL or high titres of anti-β2-glycoprotein-I on two separate occasions at least 12 weeks apart.[19] In the context of RM, adverse pregnancy outcome refers to either:

- ≥3 consecutive miscarriages <10 weeks gestation with other causes for miscarriage excluded or
- one or two losses of a normally formed fetus >10 weeks gestation.

APS treatment combines twice daily unfractionated heparin (from positive pregnancy test until at least six weeks post-partum) and daily low-dose aspirin (LDA, commencing prior to pregnancy until 34 weeks of gestation). Low molecular weight heparin (LMWH) has the benefits of once daily administration and a superior safety profile for thrombocytopenia and osteopenia. One randomised study of 60 women found that LMWH was not inferior to unfractionated heparin in RM patients with APS[20] but larger prospective trials of LMWH efficacy are needed.[21]

There has been interest in RM patients who exhibit so-called non-criteria clinical and/or laboratory manifestations of APS, for instance, low rather than moderate/high anti-phospholipid antibody titres.[22] Prospective and retrospective studies suggest that such patients could possibly benefit from LMWH plus LDA[22] but this requires testing in large prospective trials.

PARENTAL STRUCTURAL CHROMOSOMAL ABNORMALITIES

Structural chromosomal abnormalities, most commonly (~85%) balanced translocations (reciprocal translocations (~60%) and Robertsonian translocations (~40%)) are found in 2–5% of RM couples (Table 2) compared with 0.7% of the general population.[2,12,23,24] Parental karyotyping is recommended by the ASRM and the DGGG/OEGGG/SGGG.[7,8] The RCOG proposed selective karyotyping depending on whether an unbalanced arrangement is found in the products of conception.[5]

Patients with chromosomal abnormalities should be referred for genetic counselling.[5,8] Although embryos with unbalanced chromosomal arrangements can theoretically be screened out, PGT is not routinely advised since the likelihood of a pregnancy with an unbalanced karyotype surviving into the second trimester is low (0.8% in one study[23]) and overall livebirth rates have not been shown to be higher with IVF/PGT compared with natural conception.[25–27] However, it remains possible that PGT in couples with structural chromosomal defects might reduce the number of miscarriages experienced prior to a successful live birth,[27] but this requires further evaluation.

UTERINE STRUCTURAL ABNORMALITIES

Congenital (septate, bicornuate, unicornuate, didelphys and arcuate defects) and acquired (fibroids, polyps and adhesions) uterine defects are frequently identified in RM patients (Table 2).[2] In one study of over 900 RM patients, uterine anomalies were identified in 19.5% of patients with 6.2% and 13.3% being congenital and acquired, respectively.[28] An assessment of uterine anatomy is therefore recommended for patients with RM.[5] Two-dimensional (2-D) ultrasonography with or without saline infusion (sonohysterography) usually constitutes first-line investigations. The Thessaloniki ESHRE/ESGE consensus group recommended 3-D ultrasonography for investigating uterine anomalies in high-risk patients, and magnetic resonance imaging and endoscopic examinations for suspected complex malformations or diagnostic difficulties.[29]

Uterine septae

Uterine septae were the commonest congenital abnormalities identified in ~5% of RM women in one series.[28] Since the change from abdominal to hysteroscopic surgical approaches, uterine septae have become amenable to low-risk surgical correction (Fig. 1).[7,30,31] Pooled analyses of 14 studies involving 1324 women undergoing hysteroscopic resection identified 15 perforations (1.1%) and two cervical lacerations (0.1%).[32]

Retrospective studies consistently report lower miscarriage rates in patients after metroplasty compared with untreated patients. A large retrospective study found that miscarriage decreased from 41.7% to 11.9% following hysteroscopic septal resection.[33] In another study involving 361 patients, the miscarriage rate decreased from 94.3% to 16.1% and livebirth rate increased from 2.4% to 75% following hysteroscopic correction.[34] However, notably there are no published randomised controlled studies evaluating septal resection.[35]

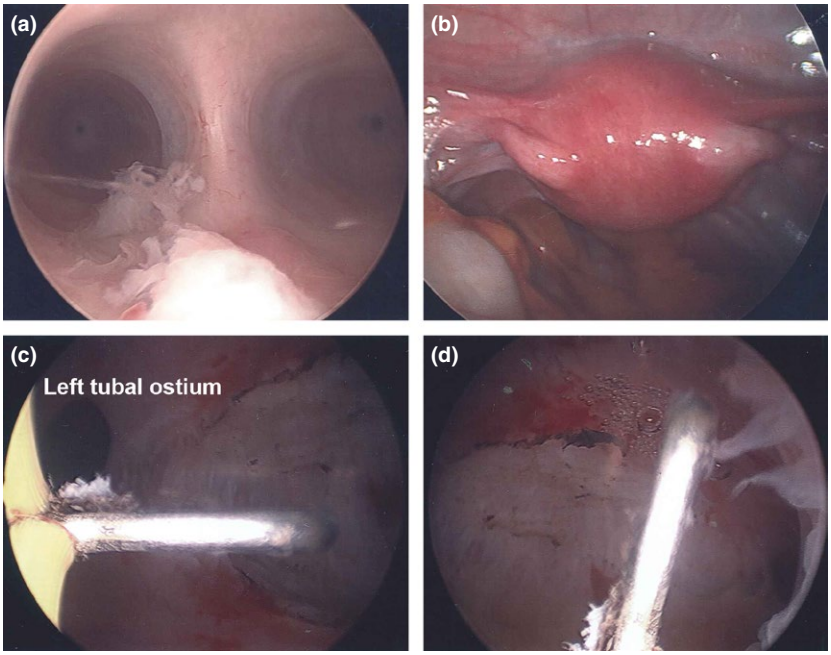

FIGURE 1 Hysteroscopic resection of uterine septum in a 33-year-old patient who had no livebirths and two spontaneous miscarriages at 11 weeks and 8–9 weeks gestation after fetal heart beats had been detected on ultrasound scan. (a and b) Pre-operative views showing septum (a) and normal external uterine fundal contour (b). (c and d) Post-resection views. Note that the cutting knife electrode (Collin's electrode) of the resectoscope is visible.

In their recent guidelines for managing uterine septae, the ASRM recommended that 'it is reasonable to consider septum incision',[31] a view supported by the DGGG/OEGGG/SGGG.[7] Until gold-standard RCT-quality evidence emerges, the growing consensus supports septal resection.

Fibroids and other acquired structural defects

An earlier systematic review found an association between fibroids and higher miscarriage rates[36] but robust prospective evidence that myomectomy reduces miscarriage is lacking.[37] It is widely acknowledged that the magnitude of effect of fibroids on pregnancy is greatest for submucous, least for subserous and intermediate for intramural fibroids. A recent systematic review[37] identified only one RCT involving hysteroscopic resection of submucous fibroids.[38] Among 30 women, miscarriage rates were 38.5% in the myomectomy group (n = 8) versus 50% in the expectant management group (n = 22) but the numbers were too small to draw conclusions.[38] One paper investigated the impact of submucous fibroids specifically in the context of RM patients;[39] among 966 RM patients, the incidence of all fibroid types was 8.2% (79/966), similar to values found in another series of RM patients (58/904; 6.4%).[28] Following hysteroscopic fibroid resection in the 25 of 79 cases with cavity distortion, mid-trimester loss decreased significantly from 21.7% to 0% while the live birth rate more than doubled from 23.3% to 52%.[39] However, in the absence of a matched no-treatment group with submucous fibroids, and given the good pregnancy prospects without intervention even after three miscarriages,[5] it is not known whether surgery was responsible for improved outcomes. There is also a lack of evidence regarding management of polyps and intrauterine adhesions in patients with RM. However, since many clinicians elect to remove cavity-distorting lesions on the basis that they could plausibly impair implantation, this is a difficult area in which to conduct RCTs.[8] Until better quality evidence emerges, the ASRM and DGGG/OEGGG/SGGG propose that it is reasonable to undertake surgical correction in cases of uterine cavity defects associated with fibroids, polyps and adhesions.[7,8,37]

INHERITED THROMBOPHILIAS

Thrombophilia refers to an increased risk of developing venous thromboembolism (VTE) and can be acquired (eg APS) or inherited.[40] Inherited thrombophilias include factor V Leiden mutation (FVL G1691A), prothrombin gene mutation (PT G20210A), protein C deficiency, protein S deficiency and anti-thrombin deficiency.[40]

Earlier associations between inherited thrombophilia and recurrent fetal loss[41] have not been confirmed in subsequent prospective analyses[42,43] and a very recent review found no evidence that thromboprophylaxis improves pregnancy outcome.[40] Moreover, a meta-analysis of eight trials involving 483 patients with previous late (≥10 weeks) or recurrent early losses found no benefit with LMWH.[44] A Cochrane review of nine studies involving 1228 women with a history of at least two unexplained miscarriages with or without thrombophilia also found no improvements with LDA, LMWH or a combination.[45]

The ongoing ALIFE2 (Anticoagulants for Living Fetuses 2) RCT will hopefully clarify guidance on LMWH use with inherited thrombophilia.[46] For the present, it is not recommended that RM patients be routinely screened for thrombophilia unless otherwise indicated due to prior VTE[7,8,18,40] or be given antithrombotic prophylaxis even if a thrombophilic defect is found.[40]

ENDOCRINE FACTORS: THYROID FUNCTION, PCOS AND PROLACTIN

While miscarriage is increased with overt hypothyroidism,[47] the association between subclinical hypothyroidism (SCH) and pregnancy loss is less clear. SCH refers to elevated thyroid-stimulating hormone (TSH) with normal free thyroxine levels.[48] Using an upper limit of 4–5 mIU/L for TSH, the prevalence of SCH in women of reproductive age is 4–8%.[49] One uncertainty has been whether SCH should be diagnosed in non-pregnant women trying to conceive using a lower threshold of TSH >2.5 mIU/L rather than 4 mIU/L. There are few studies of thyroid function specifically within RM populations or that have investigated pregnancy outcomes in relation to pre-pregnancy thyroid function. Two studies using a pre-pregnancy TSH threshold of 2.5 mIU/L found no association with increased miscarriage.[50,51] To date, three studies have investigated thyroxine replacement in RM patients with SCH diagnosed using TSH >2.5 mIU/L and found no improvement in either miscarriage or live birth.s[52–54] Also, in a recent large retrospective cohort study involving 5405 pregnant women with SCH, thyroxine replacement was associated with reduced miscarriage only in those with TSH >4 mIU/L and not if TSH was 2.5–4 mIU/L.[55] There are no RCTs examining the impact of thyroxine in RM women with SCH. Thus, there is a lack of evidence that SCH diagnosed at a lower threshold of TSH >2.5 mIU/L predisposes to miscarriage in RM patients or that thyroxine improves outcomes. Data from non-RM patients do suggest that for SCH diagnosed at TSH >4 mIU/L, thyroxine treatment could be beneficial. Current recommendations therefore support thyroxine for TSH >4 mIU/L but not at TSH of 2.5–4 mIU/L in the absence of thyroid antibodies.[56] Consistent with this, the American Thyroid Association now advises using TSH >4 mIU/L.[48]

Another uncertainty pertains to the significance of thyroid autoimmunity (antibodies to thyroid peroxidase (TPO) and/or thyroglobulin (Tg)), which is present in ~14% of reproductively aged women[57] and has been associated with increased miscarriage risk.[58,59] In one study, the prevalence of TPO-Ab positivity with unexplained RM was similar to the general population and treatment of TPO-Ab positive RM patients with thyroxine did not improve outcomes.[60] However, notably miscarriage risk may be exacerbated when thyroid autoimmunity co-exists with SCH.[61]

Consequently, the American Thyroid Association give a strong recommendation for thyroxine use with combined autoimmunity and TSH >4 mIU/L and a weak recommendation to consider thyroxine with autoimmunity and TSH >2.5 mIU/L.[48,49]

Although polycystic ovarian syndrome (PCOS) has been associated with increased miscarriage risk, perhaps related to hyperinsulinaemia and hyperandrogenaemia, there is a lack of clear evidence that PCOS predisposes to RM.[62] Furthermore, a meta-analysis found that metformin, an insulin-sensitising drug often used in PCOS patients, did not reduce miscarriage in PCOS.[63]

A single small RCT of 46 patients considered of low quality[64] found that bromocriptine treatment in RM patients with hyperprolactinaemia significantly reduced miscarriage rates.[65] Larger trials are required to clarify the potential benefit of dopamine agonists in RM patients with idiopathic hyperprolactinaemia.

IMMUNOLOGICAL FACTORS AND PROGESTERONE SUPPLEMENTATION

In over half of RM couples, all tests on the parents are normal.[3] In a recent prospective study, no abnormalities were identified in 55% of couples after strict application of the ASRM guidelines.[12] Given the critical role of immunological and inflammatory changes in implantation[66] and the importance of progesterone for inducing secretory endometrial changes and possibly promoting a favourable inflammatory milieu, there has been intense interest in immunomodulation and progesterone supplementation for RM.

Glucocorticoids, IVIg, lymphocyte immunotherapy, aspirin and heparin

Glucocorticoid treatment has produced inconsistent results in RM patients and can increase the risk of prematurity, orofacial clefts, gestational diabetes and hypertension.[7,66] A recent meta-analysis using strict criteria for defining unexplained RM found no RCTs involving prednisolone.[67] Two recent meta-analyses of intravenous immunoglobulin (IVIg) use in RM found no evidence of improved live birth rates.[67,68] Recent meta-analyses of allogenic lymphocyte immunotherapy (eg paternal lymphocyte infusion) reported improved live birth rates in the treatment arm.[69,70] However, these studies have been criticised for their low quality, low numbers of patients and lack of consistency in the patient populations recruited.[67] Finally, the available evidence from RCTs does not support the use of heparin and LDA, either alone or in combination.[45,71–74] It should also be noted that transfusion of blood products is not without potentially serious complications and that long-term heparin use risks maternal osteopenia.

Intralipid, TNF-α inhibitors and G-CSF

Intralipid is a fat emulsion used for parenteral nutrition. It has been proposed that intralipid might benefit RM by reducing peripheral blood natural killer (NK) cell activity and suppressing pro-inflammatory cytokines.[75] Intralipid has been evaluated in only one RCT that tested whether a 250 mL infusion on the day of oocyte retrieval (with further infusions if there was a positive pregnancy test) could increase chemical pregnancy rates in RM patients with elevated peripheral blood NK cells (>12%) undergoing IVF.[76] No benefit was found for the primary outcome, chemical pregnancy, although increased rates of ongoing pregnancies and live birth rates were observed, the significance of which requires further investigation by appropriately powered studies.

Tumour necrosis factor (TNF)-α is a proinflammatory cytokine produced by T-helper 1 cells and can be neutralised using anti-TNF-α drugs such as adalimumab (Humira®). One small retrospective study found improved live birth rates when anti-TNF-α was combined with other regimes that included heparin, LDA and/or IVIg.[77] However, there are no well-designed prospective studies of anti-TNF-α use in RM patients.

Granulocyte colony-stimulating factor (G-CSF) is a cytokine produced by decidual cells that stimulates granulocyte proliferation and differentiation. One small RCT of 68 women with unexplained RM found that G-CSF treatment (administered subcutaneously from the sixth day after ovulation to the ninth week of gestation) increased live birth rates from 48% in the placebo group to 83% in the treatment group.[78] More recently, a pilot RCT found no benefit following intrauterine G-CSF administration in unexplained RM.[79]

Progesterone

The Progesterone in Recurrent Miscarriage (PROMISE) trial involved 836 women with idiopathic RM randomised to receive either 400 mg of vaginal micronised progesterone (Utrogestan®) twice daily or placebo from the time of positive pregnancy test to 12 weeks gestation.[80] There was no difference between the two groups in miscarriage or live birth rates. In contrast, another RCT involving 700 women also tested whether the same dose of vaginally administered natural progesterone (Prontogest®) would benefit unexplained RM patients, but unlike the PROMISE trial, that trial commenced treatment in the luteal phase immediately after documentation of ovulation using either ultrasound or luteinising hormone (LH) kits and continued until 28 weeks gestation.[81] This Egyptian trial found significantly lower miscarriage rates (12.4 vs 23.3%) and higher live birth rates (92% vs 77%) in the treated group.[81]

A meta-analysis of 10 RCTs (including the PROMISE trial) involving 1586 women with idiopathic RM evaluated the effects of natural and synthetic progesterones administered during the first trimester and commenced after pregnancy confirmation.[82] Lower miscarriage and higher live birth rates were found in the eight studies that used synthetic progesterones.[82] However, included studies spanned more than 60 years, and multiple formulations, dosages and administration routes were used making it difficult to recommend any particular regime.[82]

Collectively, these data suggest that progesterone is likely beneficial in unexplained RM. Synthetic progesterone may be superior to natural progesterone, at least when progesterone is commenced after a positive pregnancy test. However, formulation, dosage and route of administration need to be defined. Natural progesterone may be beneficial but should be started in the luteal phase with consideration given to continuing beyond the first trimester.

OTHER FACTORS: TLC, INFECTION, LIFESTYLE AND SPERM DNA DAMAGE

It is widely accepted that psychological support in a dedicated RM clinic setting complemented with weekly ultrasound scanning (so-called TLC (tender-loving care)) is beneficial.[8,83,84] Bacterial vaginosis (BV) is associated with second trimester miscarriage[85] but prospective evidence linking BV or other infective agents with recurrent early pregnancy loss is lacking.[8,85–87] Patients should be advised that modifiable factors such as obesity, coffee, alcohol, smoking and cocaine use have been linked with increased miscarriage risk.[7,8] Eliminating smoking and alcohol and optimising body mass index would benefit not only miscarriage but also the risk profile for later pregnancy. Increased semen abnormalities such as DNA fragmentation and aneuploidy have been found in RM couples[88,89] but at this stage, such abnormalities cannot be considered predictive of an increased risk of RM.

CONCLUSION

Recurrent miscarriage is a complex condition requiring consideration of multiple factors for appropriate workup and management (Table 3). The decision to intervene depends on the benefit-to-risk ratio of proposed treatment. APS, uterine structural defects and structural chromosomal abnormalities are the parental pathologies most strongly tied to RM. The benefit of combined unfractionated heparin and LDA in APS is supported by robust prospective evidence. However, further investigation of LMWH efficacy and treatment for non-criteria APS are required. Septal resection is not risk-free but in trained hands, is low-risk. The available evidence supports surgical correction of the septum but is limited to retrospective studies and therefore subject to bias. Similar considerations apply to other uterine cavity defects, fibroids, polyps and adhesions. After appraising the evidence, the ASRM concluded that it is reasonable to consider surgical correction for septae and cavity-distorting fibroids.[31,37] It is recommended that thyroxine be used for TSH >4 mIU/L. If thyroid autoimmunity co-exists, when thyroxine may be considered at TSH >2.5 mIU/L. Thrombophilia screening is no longer recommended.

TABLE 3 Summary of current evidence regarding RM management

Condition	Supported by currently available evidence and expert opinion	Notes
APS	Unfractionated heparin and low-dose aspirin	Further investigation required for LMWH and non-criteria APS
Uterine septum	Hysteroscopic resection	RCT evidence awaited
Submucous fibroids, polyps and adhesions	Hysteroscopic resection	RCT evidence awaited
Structural chromosomal rearrangements	Genetic counselling	Lack of evidence that IVF with PGT improves chances of livebirth
Thyroid function	Thyroxine treatment for TSH > 4 mIU/L ± anti-thyroid antibodies	Consider thyroxine for TSH > 2.5 mIU/L + anti-thyroid antibodies
Inherited thrombophilia	Screening is not recommended	
Unexplained RM	Treatment for immune factors is not recommended	Lack of standardised diagnostic criteria for specific immunological conditions
	Progesterone likely to be beneficial	Consider synthetic versus natural, time of commencement and duration of use
Embryonic chromosomal abnormalities	Karyotyping of products of conception is informative	Provides a strong indication of likelihood of finding a parental abnormality and helpful in providing an explanation for couples
		Lack of evidence that IVF with PGT increases chances of livebirth
Psychological support	Tender loving care (TLC)	Patients find dedicated RM clinics with regular ultrasound scanning very helpful

APS, antiphospholipid syndrome; IVF, in vitro fertilisation; LMWH, low molecular weight heparin; PGT, preimplantation genetic testing; RCT, randomised controlled trial; RM, recurrent miscarriage; TSH, thyroid-stimulating hormone.

The most difficult question is what should be done in the more than 50% of RM cases in which all the couple's investigations are normal? Patients can be reassured that the cumulative chances of a successful pregnancy within five years are 60–75% with supportive care alone.[90,91] Progesterone treatment carries low risk and, in this situation, evidence from a large RCT[81] and a recent meta-analysis[82] suggests it is likely to be beneficial. While deregulated maternal immune tolerance could plausibly contribute, as yet, there are no pathognomonic diagnostic criteria for reproducibly identifying a distinct immunological entity. An RCOG Scientific Impact Paper devoted entirely to NK cells concluded that measurement of peripheral blood NK cells 'are of limited value in aiding our understanding of the role of uterine NK cells in reproductive failure' and that 'the measurement of uterine NK cells must be standardised'.[92] Without standardised diagnostic criteria, it is not possible to clearly identify whom should be treated. Combined with a lack of evidence of benefit and substantial associated risks in many cases, no authorities advocate immune treatments. Finally, clinicians should remain cognisant of the contribution from embryonic aneuploidy. Chromosomal analyses of miscarriage products can provide an explanation in many cases and when normal, markedly increase the likelihood of underlying parental pathology.

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