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RCOG GREEN-TOP GUIDELINES

Recurrent Miscarriage

Green-top Guideline No. 17

Lesley Regan | Rajendra Rai | Sotirios Saravelos | Tin-Chiu Li | on behalf of the Royal College of Obstetricians and Gynaecologists

Correspondence
Royal College of Obstetricians and Gynaecologists, 10–18 Union Street, London SE1 1SZ, UK.
Email: clinicaleffectiveness@rcog.org.uk

This is the fourth edition of this guideline, which was published in 1998 and 2003 under the title *The Investigation and Treatment of Couples with Recurrent Miscarriage*. The third edition was published in 2011 under the title *The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage*.

Key recommendations

- In this guideline, recurrent miscarriage has been defined as three or more first trimester miscarriages. However, clinicians are encouraged to use their clinical discretion to recommend extensive evaluation after two first trimester miscarriages, if there is a suspicion that the miscarriages are of pathological and not of sporadic nature.
- Women with recurrent miscarriage should be offered testing for acquired thrombophilia, particularly for lupus anticoagulant and anticardiolipin antibodies, prior to pregnancy. [Grade C]
- Women with second trimester miscarriage may be offered testing for Factor V Leiden, prothrombin gene mutation and protein S deficiency, ideally within a research context. [Grade C]
- Inherited thrombophilias have a weak association with recurrent miscarriage. Routine testing for protein C, antithrombin deficiency and methylenetetrahydrofolate reductase mutation is not recommended. [Grade C]
- Cytogenetic analysis should be offered on pregnancy tissue of the third and subsequent miscarriage(s) and in any second trimester miscarriage. [Grade D]
- Parental peripheral blood karyotyping should be offered for couples in whom testing of pregnancy tissue reports an unbalanced structural chromosomal abnormality [Grade D] or there is unsuccessful or no pregnancy tissue available for testing. [GPP]
- Women with recurrent miscarriage should be offered assessment for congenital uterine anomalies, ideally with 3D ultrasound. [Grade B]
- Women with recurrent miscarriage should be offered thyroid function tests and assessment for thyroid peroxidase (TPO) antibodies. [Grade C]
- Women with recurrent miscarriage should not be routinely offered immunological screening (such as HLA, cytokine and natural killer cell tests), infection screening or sperm DNA testing outside a research context. [Grade C]
- Women with recurrent miscarriage should be advised to maintain a BMI between 19 and 25 kg/m^2, smoking cessation, limit alcohol consumption and limit caffeine to less than 200 mg/day. [Grade D]
- For women diagnosed with antiphospholipid syndrome, aspirin and heparin should be offered from a positive test until at least 34 weeks of gestation, following discussion of potential benefits versus risks. [Grade B] Aspirin and/or heparin should not be given to women with unexplained recurrent miscarriage. [Grade B]

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- There are currently insufficient data to support the routine use of PGT-A for couples with unexplained recurrent miscarriage, while the treatment may carry a significant cost and potential risk. [Grade C]
- Resection of a uterine septum should be considered for women with recurrent first or second trimester miscarriage, ideally within an appropriate audit or research context. [Grade C]
- Thyroxine supplementation is not routinely recommended for euthyroid women with TPO who have a history of miscarriage. [Grade A]
- Progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (for example 400 mg micronised vaginal progesterone twice daily at the time of bleeding until 16 weeks of gestation). [Grade B]
- Women with unexplained recurrent miscarriage should be offered supportive care, ideally in the setting of a dedicated recurrent miscarriage clinic. [Grade C]

1 | PURPOSE AND SCOPE

The purpose of this guideline is to provide guidance on the investigation and care of women and people with recurrent miscarriage.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth. The term couple is used to describe two individuals trying to conceive, recognising that in some instances these individuals may not be in a relationship. While every effort is made to ensure the RCOG uses inclusive language there are instances where we have been unable to adhere to this, for example where original research is being referenced the language within the publication is used for accuracy.

2 | INTRODUCTION AND BACKGROUND EPIDEMIOLOGY

Miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. It should be noted that advances in neonatal care have resulted in more babies surviving birth before 24 weeks of gestation.

There are two types of miscarriage: sporadic and recurrent. Sporadic miscarriage (occurring most commonly in the first trimester) is often the result of random fetal chromosomal anomalies.[1,2] Its incidence increases with age and may affect between 10% and 50% of women aged 20 to 45 years respectively.[3] By contrast, recurrent miscarriage has traditionally been defined as three or more miscarriages affecting approximately only 1% of women.[4,5] A similar incidence of approximately 1% is also the case for women experiencing a second trimester miscarriage, where random fetal chromosomal anomalies are significantly lower.[6]

Several features suggest that recurrent miscarriage is a distinct clinical entity rather than just three incidental sporadic miscarriages occurring by chance: i) a woman's risk of miscarriage is directly related to the outcomes of previous pregnancies, ii) the average observed incidence of recurrent miscarriage is higher than what would be expected by chance alone, and iii) unlike sporadic miscarriage, recurrent miscarriage tends to occur even if the fetus has no chromosomal anomalies.[5]

Overall, the greatest determinant of the incidence of recurrent miscarriage is age,[7] while the number of previous miscarriages affects the chance of a live birth across all age groups.[8]

The incidence of recurrent miscarriage would more than double if two miscarriages were used for the definition, as the pooled risk has been shown to be 1.9% (1.8–2.1%) for two miscarriages and 0.7% (0.5–0.8%) for three miscarriages.[9]

It is worth noting that at the time of writing these guidelines a Lancet Series of three articles dedicated to miscarriage was published, which challenged the traditional approach and distinction of care between sporadic and recurrent miscarriage. It criticised any pervasive attitude of acceptance towards sporadic miscarriage and called for worldwide reform that would improve the support and care of women and their partners after one miscarriage (not just after three).[9–12]

In the Series, the authors proposed a graded model of care, where after one miscarriage women would have their health needs evaluated and would be provided with information and guidance to support future pregnancies. If a second miscarriage were to occur, they would be offered an appointment at a miscarriage clinic for initial investigations, extra support and early reassurance scans for subsequent pregnancies. Finally, after three miscarriages they would be offered a full series of evidence-based investigations and care, as described in guidelines such as these.[9–12]

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Although the care of women and couples after sporadic miscarriages is outside of the remit of this guideline, the model should be encouraged as it appears to bridge the gap between sporadic and recurrent miscarriage care, encouraging a systematic graded approach rather than a fragmented one. It also addresses the balance between the need for evidence-based and supportive care, while targeting healthcare resources effectively.

3 | DEFINITIONS AND TERMINOLOGY

The terminology and definitions used in reference to recurrent miscarriage vary considerably. The American Society for Reproductive Medicine (ASRM) have used the term recurrent pregnancy loss[13] and have recommended clinical evaluation after two first trimester clinical pregnancy losses (i.e. those documented by ultrasonography or histopathological examination). However, they have recommended a threshold of three or more losses for epidemiological studies.[14]

The European Society for Human Reproduction and Embryology (ESHRE) have described, in their 2017 guideline, a discrepancy in opinions among their guideline group members and concluded with a definition of two or more pregnancy losses.[15]

In this guideline, recurrent miscarriage has been defined as three or more first trimester miscarriages, in keeping with the previous RCOG guidelines. However, clinicians are encouraged to use their clinical discretion to recommend extensive evaluation after two first trimester miscarriages, if there is a suspicion that the miscarriages are of pathological and not of sporadic nature (for example if a woman has had a pregnancy loss with a normal non-invasive prenatal test or karyotype). Owing to the fact that the incidence of certain diagnoses does not appear to differ between women with consecutive versus non-consecutive losses, the definition in the present guideline has not been restricted to women suffering with consecutive miscarriages only.[16,17] In addition, it is not restricted to miscarriages suffered with the same partner, as certain maternal pathologies would be unaffected by the partner.

4 | IDENTIFICATION AND ASSESSMENT OF EVIDENCE

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched looking for the following terms in the title or abstract 'spontaneous abortion', 'miscarriage', 'pregnancy loss', 'consecutive miscarriage', 'risk factors', 'prenatal care', and 'pregnancy care'. The search was restricted to articles published until November 2021, while additional key references were added during the review process. The full search strategy is available to view online as supporting information (Appendix S1 and S2).

This guideline was developed using the methodology described in the RCOG handbook *Developing a Green-top Guideline: Guidance for developers*.

5 | RISK FACTORS FOR RECURRENT MISCARRIAGE

A list of risk factors where the chance of miscarriage has been quantified by studies is shown in Appendix 2. These are further described below.

5.1 | Epidemiological factors

Advancing maternal age is associated with a decline in both the number and quality of the remaining oocytes, resulting in higher rates of aneuploidy in the fertilised embryos. A large prospective register linkage study estimated the age-related

TABLE 1 Risk table epidemiological factors.

Risk factors	Association	Evidence level	Strength
Advancing maternal age	Increased risk of miscarriage	2++	B
Advancing paternal age	Increased risk of miscarriage, although not as markedly as with maternal age	2++	B
Number of previous miscarriages	Increased risk of subsequent miscarriage	2++	B
Previous live birth	No association with subsequent miscarriage risk	2+	C
Black ethnic background	Increased risk of miscarriage	2+	D
Consanguineous relationship	No increased risk of recurrent miscarriage	2–	D
Smoking	Increased risk of miscarriage	2+	D
Excess alcohol consumption	Increased risk of miscarriage	2+	D
Excess caffeine consumption	Increased risk of miscarriage	2++	B
Women with BMI < 19 or BMI > 25 kg/m^2	Increased risk of recurrent miscarriage	2++	B
Environmental chemical exposure and dietary intake	There are limited studies examining this association and the effects of these need to be further investigated	2–	D

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risk of miscarriage to be: 12–19 years, 13%; 20–24 years, 11%; 25–29 years, 12%; 30–34 years, 15%; 35–39 years, 25%; 40–44 years, 51%; and 45 or more years, 93%.[3] *[Evidence level 2++]*

A meta-analysis has also reported increased miscarriage rates for men aged over 40 years, although far less pronounced when compared with the effect of increased maternal age.[18] *[Evidence level 2++]*

A systematic review has reported the miscarriage rates to be 11.3%, 17.0%, 28.0%, 39.6%, 47.2% and 63.9% for women with no, one, two or three, four, five and six previous miscarriages respectively.[19] *[Evidence level 2++]*

In two studies, primary versus secondary (those with a previous live birth) recurrent miscarriage did not result in a significantly different future prognosis.[20,21] *[Evidence level 2+]*

A large observational study found that compared with white Europeans, the odds of a sporadic miscarriage were increased in Black African and Black Caribbean women.[22] *[Evidence level 2+]*

Observational studies have not demonstrated an association between consanguinity and recurrent miscarriage.[23,24] *[Evidence level 2–]*

Smoking has been shown to increase the risk of sporadic miscarriage.[25] *[Evidence level 2+]*

An observational database study found an increased risk of spontaneous miscarriage in the first trimester for women consuming five or more alcoholic drinks/week (approximately 10 units/week).[26] *[Evidence level 2+]*

Similarly, there is some evidence for an association between increased caffeine intake and sporadic miscarriage.[27] *[Evidence level 2++]*

Observational studies have reported that obesity increases the risk of sporadic miscarriage.[28–30] In the meta-analysis of Ng et al. (2021) women with a BMI below 19 and above 25 kg/m^2 were at higher odds of recurrent miscarriage.[31] *[Evidence level 1+]*

The association between environmental risk factors (such as air pollution and household chemicals) and pregnancy loss is based mainly on women with sporadic rather than recurrent miscarriage.[32] The results are limited by difficulties in controlling for confounding factors, reporting of data on exposure and the measurement of toxin dose. Nevertheless, awareness of a potential adverse association should be raised and future well conducted studies should be encouraged. *[Evidence level 2–]*

A number of small studies have assessed dietary variables such as selenium,[33,34] vitamin D[35] and vitamin B12[36] specifically in the population with recurrent miscarriage, although no definitive or clinically altering conclusions can be drawn. *[Evidence level 2–]*

5.2 | Thrombophilia

5.2.1 | Acquired

Antiphospholipid syndrome (APS) is defined as the association between antiphospholipid (aPL) antibodies (lupus anticoagulant, anticardiolipin [aCL] antibodies and anti-beta-2-glycoprotein-I antibodies) and adverse pregnancy outcome or vascular thrombosis.[37,38]

TABLE 2 Risk table acquired thrombophilia.

Risk factor	Association	Evidence level	Strength
Antiphospholipid antibodies	Increased risk of recurrent miscarriage, particularly for lupus anticoagulant and anticardiolipin antibodies	2++	B

Adverse pregnancy outcomes include:

- three or more consecutive miscarriages before 10 weeks of gestation;
- one or more morphologically normal fetal losses after the tenth week of gestation;
- one or more preterm births before 34^{+0} weeks of gestation because of placental disease.

In a meta-analysis including a total of 25 studies examining the association between the various aPL and recurrent miscarriage[39]: *[Evidence level 2++]*

- Lupus anticoagulant was found to have the strongest association with recurrent miscarriage (OR 7.79; 95% CI 2.30–26.45).
- IgG and IgM aCL antibodies were found to have the second strongest association with recurrent miscarriage, with odds ratios of 3.57 (95% CI 2.26–5.65) and 5.61 (95% CI 1.26–25.03) respectively.
- Anti-beta-2-glycoprotein-I antibodies showed a trend towards a positive association, but this did not reach statistical significance (OR 2.12, 95% CI 0.69–6.53) prompting the authors to recommend further studies to clarify the role of anti-beta-2-glycoprotein-I antibodies in recurrent miscarriage.

There are limited data on using clinical assays of other aPL (such as phosphatidic acid, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl inositol and phosphatidyl serine) and preliminary studies do not suggest an additional value or sensitivity in diagnosis associated with their use.[40] In addition, the lack of laboratory standardisation of these clinical assays may lead to confusion and overdiagnosis of APS. *[Evidence level 3]*

5.2.2 | Inherited

Inherited thrombophilias, including Factor V Leiden mutation, protein C and S deficiencies, antithrombin deficiency and prothrombin gene mutation, are established causes of

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TABLE 3 Risk table inherited thrombophilia.

Risk factor	Association	Evidence level	Strength
Inherited thrombophilias	There is a weak association with recurrent miscarriage.	2++	C

TABLE 4 Risk table genetic factors.

Risk factor	Association	Evidence level	Strength
Parental chromosome rearrangements	Increased risk of recurrent miscarriage	2+	C

systemic thrombosis. However, inherited thrombophilias have also been implicated as a possible cause in recurrent miscarriage and late pregnancy complications with the presumed mechanism being thrombosis of the uteroplacental circulation.

Meta-analyses of pooled data suggest that the magnitude of the association between inherited thrombophilias and fetal loss varies according to the type of thrombophilia, timing of fetal loss, maternal ethnicity and maternal age. It is generally recognised that there is a stronger and more consistent association between second trimester miscarriages and inherited thrombophilias.[41,42] *[Evidence level 2++]*

To date, the following associations have been shown through systematic reviews and meta-analyses: *[Evidence level 2++]*

- Factor V Leiden appears to be associated with first and particularly second trimester recurrent miscarriages.[41,43]
- Prothrombin gene mutation is associated with recurrent miscarriage.[41–43]
- Protein S deficiency has not demonstrated a consistent association with recurrent first trimester miscarriage, but has shown an association with second trimester.[41,44,45]
- Protein C deficiency has not shown a consistent association with recurrent miscarriage.[41,44]
- Methylenetatrahydrofolate reductase (MTHFR) mutation (heterozygous and homozygous) has been found to have a significant association with recurrent miscarriage in one meta-analysis from China.[46] However other meta-analyses did not find an association and advise against testing for this mutation.[41,47]
- Antithrombin deficiency is the rarer yet most thrombogenic mutation; however, the European prospective cohort study on thrombophilia (EPCOT) found only a possible association with sporadic miscarriage[44] while a subsequent meta-analysis did not.[41]

5.3 | Genetic factors

5.3.1 | Parental chromosomal rearrangements

The incidence of parental chromosomal rearrangements appears to be associated with recurrent miscarriage, with one large database study estimating that a translocation is present in 2.2% of parents after one miscarriage, 4.8% after two miscarriages, and 5.7% after three miscarriages.[48] Studies, however, have reported a low risk of parents with balanced translocations having a pregnancy with an unbalanced karyotype surviving into the second trimester (0.8%) or a disabled child born with an unbalanced chromosome abnormality (0.02%).[49,50] *[Evidence level 2+]*

In a study by Franssen et al.,[49] although overall the chances of parents with a balanced structural chromosome abnormality having a healthy child was found to be 83%, which was similar to the control couples (84%), the former had a higher chance of a subsequent miscarriage compared with the latter group (49% versus 30%; $P < 0.01$), something which has also been supported by other more recent studies.[51] The association between the type of parental chromosomal rearrangement and risk of subsequent miscarriage also appear dependent on the type of rearrangement, as miscarriage rates for parents with reciprocal translocations, inversions, Robertsonian translocations, and other types of chromosomal anomalies have been shown to be 54%, 49%, 34% and 27% respectively.[49] *[Evidence level 2+]*

5.3.2 | Fetal chromosomal anomalies

Chromosome anomalies of the pregnancy are the commonest cause of both sporadic miscarriage and recurrent miscarriage. A review reported that approximately 50% of sporadic miscarriages are a result of fetal chromosome anomalies (pooled prevalence 49.7%; 95% CI 34.9–64.6%). Among those with anomalies, in descending order of frequency were: trisomy (51.9%); polyploidy (18.8%); monosomy (15.2%); structural anomalies (6.5%); and others (7.6%).[52] *[Evidence level 2–]*

TABLE 5 Risk table genetic factors.

Risk factor	Association	Evidence level	Strength
Chromosome anomaly of the pregnancy	Is the commonest cause of sporadic and recurrent miscarriage	2++	B
Miscarriage of euploid pregnancy	Is associated with an increased risk of subsequent miscarriage	2+	C

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The incidence of aneuploidy in recurrent miscarriage was found to be approximately 40% (40.4%; 95% CI 25.2–55.7%), suggesting that non-genetic factors may play a more important role in recurrent miscarriage.[53] A study has shown that miscarriages following assisted reproductive treatment have rates of cytogenetic anomalies similar to sporadic miscarriages (56.8% versus 53.6%; OR 1.11, 95% CI 0.71–1.73).[52] *[Evidence level 2++]*

It is worth noting that with newer molecular techniques a further 5–7% submicroscopic variants may also be detected.[52,54] This may be reflected by the fact that newer studies using microarray techniques have been reporting even higher number of cytogenetic anomalies in women with sporadic miscarriages of up to 59.4% (1106/2389).[55] *[Evidence level 2++]*

When examining missed miscarriages with a normal karyotype, embryoscopic studies have also shown a further 18% of fetuses to have morphological defects,[56] although it cannot be ascertained whether this is a result of maternal factors or fetal genetic anomalies not evident on traditional karyotyping. *[Evidence level 2+]*

Studies have shown that the higher the number of euploid miscarriages, the higher the chance of a subsequent miscarriage,[57] presumably owing to the higher chance of a persistent maternal pathology rather than a sporadic aneuploidy. Equally, a finding of an aneuploid embryo has been found to confer an improved prognosis in the subsequent pregnancy.[58,59] This is assuming that the women are age adjusted, as an older woman with an aneuploid loss may still have a worse prognosis compared with a younger woman with a euploid loss. It may also not be the case with parental chromosome anomalies, as the embryonic aneuploidy in these cases is secondary to parental pathology and not sporadic in nature. *[Evidence level 2+]*

5.4 | Anatomical factors

5.4.1 | Congenital uterine anomalies

Incidence

The incidence of congenital uterine anomalies (CUAs) appears to be higher than previously thought, owing to improved diagnostic imaging modalities.[60] A systematic review and meta-analysis has estimated the prevalence to be 5.5% (95% CI 3.5–8.5%) in unselected women, 8.0% (95% CI 5.3–12%) in infertile women, 13.3% (95% CI 8.9–20.0%) in women with recurrent miscarriage and 24.5% (95% CI 18.3–32.8) in women with infertility and miscarriage. The commonest anomalies across all populations appear to be the canalisation defects (i.e. the septate variety) followed by the unification defects (i.e. the bicornuate and unicornuate variety).[61] *[Evidence level 2++]*

TABLE 6 Risk table anatomical factors.

Risk factor	Association	Evidence level	Strength
Congenital uterine anomalies	Increased risk of miscarriage with septate and bicornuate uteri	2++	B

First trimester miscarriage

In terms of reproductive outcomes, a meta-analysis has shown that the risk of sporadic first trimester miscarriage was not significantly increased in women with arcuate (RR 1.22, 95% CI 0.87–1.72; six studies), didelphys (RR 1.13, 95% CI 0.45–2.86; four studies) and unicornuate uteri (RR 1.38, 95% CI 0.83–2.28; five studies) versus normal controls.[62] *[Evidence level 2++]*

However, women with septate (RR 2.65, 95% CI 1.39–5.06; six studies) and bicornuate uteri (RR 2.32, 95% CI 1.05–5.13; four studies) had a significantly increased risk of sporadic first trimester miscarriage versus normal controls.[62] *[Evidence level 2++]*

Second trimester miscarriage

The risk of sporadic second trimester miscarriage was not significantly increased in women with didelphys (RR 1.71, 95% CI 0.63–4.59; four studies) and unicornuate uteri (RR 2.27, 95% CI 0.64–7.96; four studies) versus normal controls.[62] *[Evidence level 2++]*

However, women with arcuate (RR 1.98, 95% CI 1.06–3.69; five studies), septate (RR 2.95, 95% CI 1.51–5.77; five studies) and bicornuate uteri (RR 2.90, 95% CI 1.56–5.41; four studies) had a significantly increased risk of sporadic second trimester miscarriage versus controls.[62] *[Evidence level 2++]*

When assessing a population with recurrent miscarriage, there were not enough studies in the literature to perform a meta-analysis in terms of subtypes of anomalies or first versus second trimester miscarriages; however, the overall rate of subsequent miscarriage (first or second trimester) remained significantly increased 1.13 (1.06–1.22) compared with women with unexplained recurrent miscarriage.[62] *[Evidence level 2++]*

It is worth noting that since this meta-analysis, a large prospective study by Prior et al. (2018), using gold standard 3D ultrasound solely to diagnose the arcuate uterus (in contrast to the varying diagnostic modalities included in the studies of the meta-analysis), reported similar clinical pregnancy and live birth rates between arcuate and normal uteri.[63] Moreover, all the latest classifications on uterine anomalies (ESHRE/European Society for Gynaecological Endoscopy [ESGE], Congenital Uterine Malformation by Experts [CUME] and ASRM) consider the arcuate uterus to be a normal variant with no clinical implications, something which should be reassuring to both clinicians and patients.[64–66]

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5.4.2 | Acquired uterine anomalies

There are limited prospective case–control data evaluating the association between acquired uterine anomalies and sporadic or recurrent miscarriage.

Myomas

In a large meta-analysis of a general obstetric population, including 1394 women with myomas and 20 435 without, no increase in risk of miscarriage was found (11.5% versus 8.0%; RR 1.16, 95% CI 0.80–1.52).[67] However, the distinction between submucosal, intramural and subserosal myomas, which are known to affect fertility in varying degrees, was limited.[68] The authors concluded that failure of prior studies to adjust for confounders may have led to the common clinical belief that leiomyomas are a risk factor for miscarriage. *[Evidence level 2++]*

An analysis from prospectively collected data in a recurrent miscarriage population found a similar incidence of myomas to that reported in the general population (8.2% versus 10.4%).[69,70] However, in the recurrent miscarriage study, women with submucosal and intramural/subserosal myomas were found to have a higher proportion of second trimester miscarriages compared with women with unexplained recurrent miscarriage (21.7% and 17.6% versus 8.0% respectively; $P < 0.01$). Women with submucosal myomas undergoing resection had a significant reduction in second trimester miscarriage rates (21.7% to 0%; $P < 0.01$), although there was a lack of a case–control group to compare what the outcome would have been if women with submucosal myomas had not undergone resection. In the same study, women with intramural/subserosal myomas did not undergo surgery and experienced similar live birth rate compared with the unexplained recurrent miscarriage group in the subsequent pregnancy.[70] *[Evidence level 3]*

Endometrial polyps

There are no data to our knowledge specifically examining the effect of polyps on sporadic or recurrent miscarriage. Therefore, it seems reasonable to recommend management similar to that of the general population.[71]

Intrauterine adhesions

There is a plausible link between intrauterine adhesions and miscarriage, although this currently remains unsubstantiated. These include: i) constriction of the uterine cavity caused by adhesions, ii) lack of a sufficient amount of normal endometrial tissue to support implantation and development of the placenta, and iii) defective vascularisation of the residual endometrial tissue consequent upon fibrosis of endometrium.[72] *[Evidence level 3]*

A systematic review and meta-analysis has demonstrated that the incidence of intrauterine adhesions increases with the number of previous miscarriages experienced (OR 1.99, 95% CI 1.32–3.00; seven studies) and the number of previous dilatation and curettage procedures (OR 2.05, 95% CI 1.35–3.12; seven studies).[73] *[Evidence level 2++]*

This has major implications for women with recurrent miscarriage who are at risk of undergoing surgical management of miscarriage. In the meta-analysis by Hooker et al.[63] similar pregnancy outcomes were reported subsequent to conservative, medical and surgical treatment of miscarriage, although the number of studies evaluating the long-term reproductive outcome was limited and different time scales were used. Owing to a large variation in primary outcomes, methodology and populations, they were unable to perform meta-analyses on reproductive outcome after miscarriage. *[Evidence level 3]*

Small cohort studies have, however, suggested that women with intrauterine adhesions and endometrial thickness less than 5 mm have higher sporadic miscarriage rates versus women with endometrial thickness of more than 5 mm (50% versus 8.3%; $P < 0.001$).[74] *[Evidence level 3]*

TABLE 7 Risk table anatomical factors.

Risk factor	Association	Evidence level	Strength
Acquired uterine anomalies	Remains uncertain due to limitation of studies and methodological quality	3	D

5.4.3 | Cervical integrity

Causes of second trimester miscarriage appear to overlap with the causes of first trimester miscarriage on one end of the spectrum and causes of preterm birth on the other end of the spectrum. Cervical insufficiency, along with infection and congenital uterine anomalies appear to be main contributors of second trimester miscarriage.[75] Although investigations have been reported to reveal a diagnosis in only approximately 50% of cases in dedicated clinics,[76] future developments, such as in the field of the maternal microbiome may shed more light in these so far unexplained cases.[77] *[Evidence level 2–]*

The true incidence of cervical insufficiency remains unknown, since the diagnosis is clinical. There is currently no satisfactory objective test that can identify women with cervical insufficiency in the non-pregnant state. The diagnosis is usually based on a history of second trimester miscarriage, where commonly there has been painless cervical dilatation, with often intact membranes until the expulsion of the sac and a live fetus.[76] By extrapolation from data on extreme

TABLE 8 Risk table cervical integrity.

Risk factor	Association	Evidence level	Strength
Cervical insufficiency	Increased risk of second trimester miscarriage	2–	C

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preterm birth, a previous cervical cone biopsy[78] or an ultrasonographically short cervix[79] appear to significantly predispose to second trimester miscarriage. *[Evidence level 2–]*

5.5 | Endocrine

Systemic maternal endocrine disorders such as diabetes mellitus and thyroid disease have been associated with miscarriage. Women with diabetes who have high haemoglobin A1c levels in the first trimester are at risk of miscarriage and fetal malformation.[80] However, well-controlled diabetes mellitus is not a risk factor for recurrent miscarriage, nor is treated thyroid dysfunction.[81,82] The incidence of diabetes mellitus and thyroid dysfunction in women who suffer recurrent miscarriage appears similar to that reported in the general population.[83,84] *[Evidence level 2+]*

However, the incidence of subclinical hypothyroidism (SCH) (on this occasion defined as TSH more than 2.5 mIU/l) has been reported to be raised in a small observational study of women with recurrent miscarriage,[85] while data from a meta-analysis on sporadic miscarriages also suggests an association.[86] *[Evidence level 2–]*

The case appears to be the same for subclinical thyroid dysfunction associated with thyroid autoimmunity. Two systematic reviews and meta-analyses reported that the presence of thyroid antibodies was associated with an increased risk of recurrent miscarriage.[87,88] *[Evidence level 2++]*

Polycystic ovary syndrome (PCOS) has been linked to an increased risk of miscarriage but the exact mechanism remains unclear.[89] Polycystic ovarian morphology, elevated serum luteinising hormone levels or elevated serum testosterone levels do not appear to predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.[90] The increased risk of miscarriage in women with PCOS has nevertheless been attributed to insulin resistance, hyperinsulinaemia and hyperandrogenaemia. The prevalence of insulin resistance[91] and abnormal glucose tolerance test[92] appears to be increased in women with recurrent miscarriage compared with controls. An elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with recurrent miscarriage.[89] *[Evidence level 2+]*

Prolactin imbalances have been implicated in recurrent miscarriage. One study reported an increased level of prolactin in women with recurrent miscarriage versus controls,[83] while another study reported marginally lower prolactin levels in women with recurrent miscarriage who experienced a live birth versus those who miscarried.[93] A small randomised controlled trial (RCT) of 48 women with recurrent miscarriage and hyperprolactinaemia were randomised into bromocriptine versus no bromocriptine, showing significant differences in live birth (85.7% versus 52.4% respectively, $P < 0.05$).[94] Overall it appears that maintaining a normal level of prolactin may be beneficial in this context. *[Evidence level 2–]*

The diagnosis of a luteal phase defect varies significantly in the literature, making it difficult to assess. One study found a higher incidence of a luteal phase defect (midluteal progesterone less than 30 nmol/l) in women with recurrent miscarriage versus fertile controls (27% versus 11%),[84] whereas another study found no correlation between the presence of a luteal phase defect (midluteal progesterone less than 10 ng/ml) and the chance of subsequent miscarriage in 197 women with recurrent miscarriage.[95] Given the limited and inconsistent data from histological and serological examinations during the midluteal phase, molecular studies of the endometrium may prove to be more insightful. *[Evidence level 2–]*

TABLE 9 Risk table endocrine.

Risk factors	Association	Evidence level	Strength
Well controlled diabetes and thyroid disease	No increased risk of recurrent miscarriage	2+	C
SCH	Increased risk of recurrent miscarriage	2–	C
Thyroid autoantibodies	Increased risk of recurrent miscarriage	2++	B
Polycystic ovary syndrome	Increased risk of recurrent miscarriage	2–	D
Prolactin imbalances	Increased risk of recurrent miscarriage	2–	D
Luteal phase defect	Insufficient/ inconclusive evidence	2–	D

5.6 | Immune factors

5.6.1 | Peripheral

HLA

A systematic review and meta-analysis including 41 studies (of which selection bias was present in 40 studies and information bias in all studies) showed an increased risk of recurrent miscarriage in mothers carrying a HLA-DRB1*4 (OR 1.41, 95% CI 1.05–1.90), HLA-DRB1*15 (OR 1.57, 95% CI 1.15–2.14), or a HLA-E*01:01 allele (OR 1.47, 95% CI 0.20–1.81), and a decreased risk with HLA-DRB1*13 (OR 0.63,

TABLE 10 Risk table immune factors.

Risk factor	Association	Evidence level	Strength
Peripheral immune factors	Insufficient/ inconclusive evidence	2++	C

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95% CI 0.45–0.89) or HLA-DRB1*14 (OR 0.54, 95% CI 0.31–0.94). However, although associations between specific HLA alleles and HLA sharing with recurrent miscarriage were identified, the authors suggested that no consistent conclusions can be drawn since the observed ORs were relatively small and there was a high risk of selection and information bias present in the studies available.[96] *[Evidence level 2++]*

Cytokines

An imbalance in Th1/Th2 cytokines has been implicated in adverse pregnancy outcomes including recurrent miscarriage.[97] However, research into the role of cytokines in recurrent miscarriage is hampered by a number of factors including fluctuating levels, discordance between blood and endometrial levels and laboratory variability in measurement.[98] *[Evidence level 2+]*

A meta-analysis in 2008 concluded that the available data are not consistent with more than modest associations between cytokine polymorphisms and recurrent miscarriage. More recent meta-analyses have shown an association between some cytokine gene promoter polymorphisms and recurrent miscarriage but not for others.[99] Further research is required to assess the contribution that disordered cytokines make to recurrent miscarriage before routine cytokine tests can be introduced to clinical practice. *[Evidence level 2+]*

Peripheral natural killer (NK) cells

A meta-analysis of studies found that women with recurrent miscarriage versus controls had higher peripheral NK cell percentages (standardised mean difference [SMD] 1.36; 95% CI 0.04–2.69; $P = 0.04$) and higher peripheral NK cell numbers (SMD 0.81; 95% CI 0.47–1.16; $P < 0.00001$).[100] *[Evidence level 2+]*

However, the significance of increased peripheral NK cells remains debatable,[101] as they do not appear to reflect the levels in the endometrium,[102] show an intracycle, hormonal and ethnic variability,[103] and appear not to predict subsequent miscarriage in a population of women with recurrent miscarriage.[104] *[Evidence level 2+]*

5.6.2 | Uterine

Several studies reported that uterine NK cell density in the endometrium around the time of implantation was increased.[105–107] A meta-analysis in 2014 showed no significant difference between women with recurrent miscarriage and controls (SMD 0.40; 95% CI 1.24–2.04; $P = 0.63$)[100]; however, an inherent difficulty in performing systematic analysis was the lack of standardised laboratory protocol and agreed reference range. A multicentre working party later met and agreed on the standardisation of laboratory methods to measure and report uterine NK cell density,[108] based on which Chen et al. established a control reference range from fertile women and found that women with recurrent miscarriage did have significant increase of uterine NK cell density in precisely timed endometrial specimens.[109] Nevertheless, the prognostic value of uterine NK cell measurement remains unconfirmed.[106] *[Evidence level 2–]*

TABLE 11 Risk table immune factors.

Risk factor	Association	Evidence level	Strength
Uterine NK cells	Insufficient/ inconclusive evidence	2–	C

5.7 | Infective factors

A whole range of organisms have been implicated in first and second trimester miscarriage, including ureaplasma/mycoplasma, organisms causing bacterial vaginosis and chlamydia trachomatis.[110] For an infective agent to be implicated in the aetiology of recurrent miscarriage, it must be capable of persisting in the genital tract and avoiding detection or must cause insufficient symptoms to disturb the woman. Toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) and listeria infections do not fulfil these criteria and therefore routine TORCH screening should not be undertaken.[111] *[Evidence level 2+]*

TABLE 12 Risk table infective factors.

Risk factor	Association	Evidence level	Strength
Genital tract infections	Insufficient/ inconclusive evidence	2+	C

The presence of bacterial vaginosis in the first trimester of pregnancy has been reported as a risk factor for miscarriage and preterm birth.[112] A meta-analysis showed a statistically significant increase in second trimester miscarriages (OR 6.32, 95% CI 3.65–10.94).[113] However, the evidence for an association with first trimester miscarriage is inconsistent.[114,115] There are also a lack of data regarding the recurrent miscarriage population. *[Evidence level 2+]*

Chronic endometritis has also been implicated in recurrent miscarriage, although the diagnostic criteria remain controversial.[116] Using morphometric analysis to measure plasma cell count, a study found that the incidence of chronic endometritis in women with recurrent miscarriage was 10.8%, twice higher than that of fertile women (5.0%).[117] Future molecular studies on the microbiome of the uterine cavity will hopefully shed more light into the role of infections in recurrent miscarriage.[118] *[Evidence level 2+]*

5.8 | Male factors

Some studies have found some sperm parameters (such as viability, normal morphology, total progressive motility, hypo-osmotic swelling, acrosomal status, and nuclear chromatin

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TABLE 13 Risk table male factors.

Risk factor	Association	Evidence level	Strength
Increased sperm DNA fragmentation	Increased risk of recurrent miscarriage	2++	C

decondensation) to be lower in men experiencing recurrent miscarriage versus controls.[119–121] However, this has not been reproduced in other studies.[122,123] *[Evidence level 2+]*

The rates of anti-sperm antibodies have not been consistently shown to be increased in women and men with recurrent miscarriage, with some studies showing a higher incidence,[124] while others have not.[125] *[Evidence level 2+]*

The data are more consistent with regard to the association between abnormal sperm DNA parameters such as sperm DNA fragmentation, nuclear chromatin decondensation, and sperm aneuploidy and miscarriage. A meta-analysis in couples undergoing assisted reproduction treatment showed a significant increase in miscarriage where high sperm DNA damage was identified compared with those with low DNA damage (RR 2.16; 95% CI 1.54–3.03, $P < 0.00001$).[126] This was confirmed in a meta-analysis 2 years later.[127] This association has also been shown for the recurrent miscarriage population.[128–131] *[Evidence level 2++]*

To date, however, limited studies are available evaluating interventions that may affect sperm DNA fragmentation such as lifestyle modification (smoking cessation, weight loss/exercise, reduction in pollutant exposure), treatment of infections, control of diabetes, treatment of varicocele, antioxidant therapy, sperm selection and others.[132]

6 | WHAT ARE THE RECOMMENDED INVESTIGATIONS FOR RECURRENT FIRST TRIMESTER AND ONE OR MORE SECOND TRIMESTER MISCARRIAGES?

6.1 | Thrombophilias

6.1.1 | Acquired

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should be offered testing for acquired thrombophilia, particularly for lupus anticoagulant and anticardiolipin antibodies, prior to pregnancy.	**2++**	**C**	Given the association with recurrent miscarriage and the evidence of potential benefit from treatment.

To diagnose APS it is recommended that the woman should have two positive tests at least 12 weeks apart (and at least 6 weeks post miscarriage) for either lupus anticoagulant or aCL antibodies of IgG and/or IgM class present in medium or high titre (i.e. more than 40 GPL or MPL, or more than 99th percentile). For anti-beta-2-glycoprotein-I antibody, for which the evidence is less conclusive, IgG and/or IgM class in high titre (i.e. more than 99th percentile) can be used, within the appropriate audit or research context.[38] *[Evidence level 2++]*

In detection of lupus anticoagulant, the dilute Russell's viper venom time (dRVVT) test together with a platelet neutralisation procedure is more sensitive and specific than either the activated partial thromboplastin time (aPTT) or the kaolin clotting time (KCT) tests.[133] *[Evidence level 2++]*

Anticardiolipin antibodies are detected using a standardised enzyme-linked immunosorbent assay (ELISA). The detection of aPL is subject to considerable inter-laboratory variation.[134] This is because of temporal fluctuation of aPL titres in individuals, transient positivity secondary to infections, suboptimal sample collection and preparation, and lack of standardisation of laboratory tests for their detection. *[Evidence level 2++]*

6.1.2 | Inherited

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with second trimester miscarriage may be offered testing for Factor V Leiden, prothrombin gene mutation and protein S deficiency, ideally within a research context. They should be made aware that there is currently limited evidence that treatment changes reproductive outcomes.	**2++**	**C**	Although there is an association, there is limited evidence that treatment improves reproductive outcomes. However, some women with additional risk factors may benefit from treatment.

Testing may be offered with second trimester miscarriage for Factor V Leiden, prothrombin gene mutation and protein S deficiency[135] and, in the case of the latter, at least 6 weeks postpartum and in the absence of hormonal medication.[136] *[Evidence level 2++]*

Systematic review and meta-analyses have not found a persistent association between recurrent and/or second trimester miscarriage and protein C deficiency, antithrombin deficiency and methylenetetrahydrofolate reductase (MTHFR) mutation and therefore do not recommend testing.[41,47,136] *[Evidence level 2++]*

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Prior to testing for thrombophilia, women and people should be counselled regarding the implications for themselves and family members of a positive or negative result. The results should be interpreted by clinicians with specific expertise in the area.

6.2 | Genetic

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Cytogenetic analysis should be offered on pregnancy tissue of the third and subsequent miscarriage(s) and in any second trimester miscarriage.	**2–**	**D**	This confers significant diagnostic, psychological and auditing/research advantages.
In recurrent miscarriage, parental peripheral blood karyotyping should be performed for couples in whom testing of pregnancy tissue reports an unbalanced structural chromosomal abnormality. The finding of a subsequent abnormal parental karyotype should prompt referral to a clinical geneticist.	**3**	**D**	Retrospective studies have shown that blanket testing for parental karyotyping reveals an abnormality in less than 2%, while genetic analysis of pregnancy tissue may point towards the diagnosis.
When cytogenetic analysis is indicated but testing of the pregnancy tissue is unsuccessful or there is no pregnancy tissue available for testing, parental karyotyping should be offered.	**4**	**GPP**	With a view to achieve a diagnosis even in the absence of pregnancy tissue analysis.

Other than the prognostic advantages, when used in combination with routine investigations into recurrent miscarriage, cytogenetic analysis of the pregnancy tissue have shown to provide a diagnosis in over 90% of couples.[137] This increase in diagnoses could potentially lead to a number of advantages, such as:

- Identifying those with balanced chromosome rearrangements, who may benefit from genetic counselling and potential targeted therapies. *[Evidence level 2–]*
- Providing an answer. Not having a diagnosis has been associated with feelings of uncertainty, frustration and isolation in other fields of medicine.[138] Such adverse emotions may also be present in those who experience recurrent miscarriage. *[Evidence level 2–]*
- Reducing the chance of women and people pursuing non-evidenced based therapies (in cases where no diagnosis has been reached). *[Evidence level 4]*
- Allowing better stratification, selection and control of confounding variables for prospective research trials. *[Evidence level 4]*
- Providing further insight into the causes of miscarriage through assessing pregnancy tissue with advanced molecular studies. *[Evidence level 4]*

Techniques for analysis of pregnancy tissue

Several different techniques may apply to assess for genetic anomalies of the pregnancy, namely: conventional karyotyping via tissue culture, fluorescence in situ hybridisation (FISH), array comparative genomic hybridisation (array CGH), single nucleotide polymorphism (SNP) array and next generation sequencing (NGS). These are described in Appendix 3. *[Evidence level 4]*

A retrospective audit of four UK centres over periods of 5–30 years, reported that balanced translocations were found in 1.9% (406 out of 20 432) of parents with recurrent miscarriage, but only four unbalanced translocations were found after referral for prenatal diagnosis because of balanced parental translocation ascertained for recurrent miscarriage.[50] *[Evidence level 3]*

Although screening women (and their male partners if applicable) for parental chromosome rearrangements does not appear to be cost-effective,[50] peripheral blood karyotyping of both parents should be offered in cases where the pregnancy tissue report an unbalanced structural chromosomal abnormality. In the case where an abnormal parental karyotype is identified, genetic counselling offers the couple a prognosis for the risk of future pregnancies with an unbalanced chromosome complement and the opportunity for familial chromosome studies. *[Evidence level 4]*

Parental karyotyping may be offered when testing of the pregnancy tissue is unsuccessful or when there is no pregnancy tissue available for testing.

6.3 | Anatomical

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should be offered assessment for congenital uterine anomalies, ideally with 3D ultrasound.	**2++**	**B**	Based on evidence from meta-analyses and potential benefit from diagnosis and treatment

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An RCOG Scientific Impact Paper has been published on *Reproductive implications and management of congenital uterine anomalies*.[139] The key findings and recommendations are summarised below.

Diagnosis

A systematic review and international consensus has reported that the most accurate methodologies for diagnosing congenital uterine anomalies in descending order of overall accuracy are: 3D ultrasound (97.6%, 95% CI 94.3–100), saline-infusion ultrasound (96.5%, 95% CI 93.4–99.5), hysterosalpingography (86.9%, 95% CI 79.8–94.0) and 2D ultrasound (86.6%, 95% CI 81.3–91.8).[140] There were no studies reporting on the use of magnetic resonance imaging (MRI) as a screening tool, however comparative studies have shown MRI to be at least similar in accuracy compared with 3D ultrasound when expert examiners are used (i.e. a radiologist with an interest/expertise in gynaecological imaging).[141] *[Evidence level 2++]*

Based on these findings, acceptability and relative low cost, 3D ultrasound is recommended as the first line for the diagnosis of congenital anomalies, reserving MRI and endoscopic evaluation for complex anomalies when a diagnosis cannot be reached with 3D ultrasound.[140] *[Evidence level 2++]*

Classifications

Several classifications have been published in order to diagnose and categorise these anomalies, including the American Fertility Society (now ASRM) classification (1988),[142] the Vagina Cervix Uterus Adnexa and Associated Malformation (VCUAM) classification,[143] the embryological classification of Acien and Acien (2011),[144] the ESHRE and the ESGE classification (2013),[64] and most recently the ASRM classification (2021).[66] *[Evidence level 2++]*

Controversy regarding the septate uterus

The different classifications have been a point of contention in the literature, particularly with regards to the diagnosis of the septate uterus, the anomaly most amenable to surgical treatment. As a result, different criteria have been made for the diagnosis of the septate uterus, including a percentage of fundal cavity indentation of more than 50%,[145] a depth of fundal cavity indentation of more than 15 mm with an indentation angle of less than 90° (ASRM definition of 2016),[146] a depth of fundal cavity indentation of more than 10 mm (CUME classification),[65] and most recently a depth of fundal cavity indentation of more than 10 mm with a septum angle of less than 90° (ASRM 2021 classification).[66] *[Evidence level 2+]*

When comparing different criteria for the diagnosis of the septate uterus it is clear that the incidence changes according to criteria used,[147] with the highest incidences in descending order being from the ESHRE–ESGE to the CUME and ASRM classifications.[65] Although there are concerns of potential over-diagnosis and treatment of septate uteri by using the ESHRE–ESGE classification, there are still a lack of prospective data to determine the use of which classification would lead to the most favourable reproductive outcomes (i.e. increase in live birth rate). Therefore, which criteria should be used for the diagnosis of a septate uterus remains a matter of ongoing debate. *[Evidence level 2++]*

There is less of a debate regarding the diagnosis of other anomalies, which are more pronounced and for which there is a less variability between different classifications.

Although there is a lack of studies demonstrating a clear link between acquired uterine anomalies and recurrent miscarriage, these can be opportunistically diagnosed during the assessment for congenital uterine anomalies and treated accordingly on an individual basis (e.g. if there is associated symptomatology). The inclusion of saline infusion with the 3D ultrasound assessment may be particularly useful for the diagnosis of intrauterine adhesions if these are suspected based on the clinical history (e.g. prior surgical management of miscarriage with subsequent oligomenorrhoea).[148] *[Evidence level 4]*

6.4 | Endocrine

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should be offered thyroid function tests and assessment for thyroid peroxidase (TPO) antibodies.	**1–**	**C**	Treatment of abnormal thyroid function may confer a benefit.

Meta-analyses have reported a significant association between TPO antibodies, thyroid dysfunction and recurrent miscarriage.[87,88] *[Evidence level 1–]*

Although the presence of TPO antibodies in euthyroid women may not warrant treatment, knowing the antibody status allows for the stratification of women and people who will require thyroid function monitoring during pregnancy.[149] It is interesting to note that for women with previous miscarriages, the American Thyroid Association has given different recommendations for treatment according to the TSH levels and presence or not of autoimmunity,[150,151] while RCOG Scientific Impact Paper No. 70 on *Subclinical hypothyroidism and antithyroid autoantibodies in women with subfertility or recurrent pregnancy loss* has not.[149] The RCOG Scientific Impact Paper has also noted that performing routine preconception TPO antibody testing (alongside thyroid function tests) for women with recurrent miscarriage versus regular thyroid function tests starting in early pregnancy, are both acceptable strategies until clinical and cost-effectiveness analyses are available.[149] *[Evidence level 2++]*

Other endocrine assessments are not routinely indicated unless there is a clinical suspicion of pathology e.g. diabetes and hyperprolactinaemia.

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6.5 | Immune

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should not be routinely offered immunological screening (such as HLA, cytokine and NK cell tests), outside of a research context.	**2–**	**C**	There is a lack of consistent association between various immunological tests and recurrent miscarriage.

6.6 | Infective

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should not be routinely offered infection screening outside of the research context.	**2–**	**C**	There is a lack of consistent association between infection testing, associated treatment, and recurrent miscarriage.

The PREMEVA multicentre double-blind RCT of 84 530 pregnant women screened for bacterial vaginosis. Systematic screening and subsequent treatment for bacterial vaginosis in women with low-risk pregnancies showed no evidence of risk reduction of late miscarriage or spontaneous very preterm birth.[152] *[Evidence level 2–]*

Prospective observational studies have suggested a higher subsequent miscarriage rate in women with recurrent miscarriage and untreated chronic endometritis versus no endometritis or treated endometritis,[153,154] however well-designed prospective RCTs are lacking. *[Evidence level 2–]*

6.7 | Male factors

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Couples with recurrent miscarriage should not be routinely offered sperm DNA testing outside of the research context.	**4**	**D**	Although there appears to be an association between sperm DNA fragmentation and miscarriage, there are yet to be any prospective trials demonstrating improved outcomes with intervention.

Although there appears to be an association between sperm DNA fragmentation and miscarriage, there is a lack of prospective trials examining relevant interventions in couples with recurrent miscarriage. However, taking a detailed history from the male partner to elicit risk factors for poor sperm quality and screening for DNA fragmentation within the appropriate research context may help elucidate whether and how this information may be useful for patient counselling and for guiding clinical management.[155,156] *[Evidence level 4]*

7 | WHAT ARE THE TREATMENT OPTIONS FOR RECURRENT FIRST AND SECOND TRIMESTER MISCARRIAGES?

7.1 | Lifestyle modifications

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with recurrent miscarriage should be advised to maintain a BMI between 19 kg/m^2 and 25 kg/m^2, smoking cessation, limit alcohol consumption and limit caffeine to less than 200 mg/day.	**2–**	**D**	Observational studies show that change in lifestyle is associated with improved outcomes.

A meta-analysis of prospectively collected data in a recurrent miscarriage has shown an association between BMI and subsequent miscarriage.[31,157] Studies on sporadic miscarriage have shown associations with smoking,[25,158] alcohol[26,159] and caffeine.[27,160,161] These findings can be extrapolated on to populations of women and people with recurrent miscarriage. *[Evidence level 2–]*

There are no studies assessing the dietary intake of certain foods, antioxidants, vitamins, supplements and others in the recurrent miscarriage population. Overall in view of the limited data focusing specifically on couples with recurrent miscarriage, it seems reasonable to advise a diet similar to that recommended for any couple attempting to conceive.[162] *[Evidence level 2–]*

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7.2 | Thrombophilias

7.2.1 | Acquired

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Aspirin and heparin (unfractionated heparin [UFH] or LMWH) should be offered to women with APS (e.g. 75 mg aspirin orally and 40 mg subcutaneously enoxaparin from a positive pregnancy test until at least 34 weeks of gestation). Clinicians and women should be aware that treatment with heparin, particularly UFH, is not without some risk.	1+	B	Meta-analyses have demonstrated that treatment of APS with aspirin and heparin confers a significant benefit.
Aspirin and/or heparin should not be given to women with unexplained recurrent miscarriage	1+	B	Meta-analyses have shown it does not improve outcomes and may be associated with adverse effects.

A high quality meta-analysis of RCTs assessed pregnancy outcomes for women with recurrent miscarriage and APS who were treated with aspirin, steroids, intravenous globulin and heparin. It showed that the only treatment or treatment combination that lead to a significant increase in the live birth rate was aspirin with unfractionated heparin (UFH) infusion.[163] This treatment combination significantly reduced the miscarriage rate by 54% (aspirin plus UFH versus aspirin alone RR 0.46, 95% CI 0.29–0.71). Two further meta-analyses showed similar reduction in recurrent miscarriage for the aspirin and UFH group (OR 0.26, 95% CI 0.14–0.48).[164] The meta-analysis did not show a significant reduction in miscarriage rates in aspirin plus low molecular weight heparin (LMWH) group, but commented that further investigation is required. A 2015 Bayesian network meta-analysis also confirmed the above findings.[165] *[Evidence level 1+]*

Two prospective studies and one RCT, however, reported no difference in efficacy and safety between UFH or LMWH when combined with aspirin in the treatment of women with recurrent miscarriage associated with aPL.[166,167] In addition, a 2020 meta-analysis reported improvements in live birth with both UFH and LMWH in combination with aspirin.[168] *[Evidence level 1+]*

There are no adverse fetal outcomes reported in the meta-analysis of RCTs of low dose aspirin for the prevention of pre-eclampsia in pregnancy.[169] Heparin does not cross the placenta and hence there is no potential to cause fetal haemorrhage or teratogenicity.[170] UFH can, however, be associated with maternal complications including bleeding, hypersensitivity reactions, and heparin-induced thrombocytopenia and when used long term, osteopenia and vertebral fractures. Two prospective studies have shown, however, that the loss in bone mineral density at the lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs normally during pregnancy.[171,172] *[Evidence level 1+]*

LMWH is as safe as UFH with potential advantages during pregnancy, since they cause less heparin-induced thrombocytopenia, can be administered once daily, and are associated with a lower risk of heparin-induced osteoporosis.[173] *[Evidence level 1+]*

Pregnancies associated with APS treated with aspirin and heparin remain at high risk of complications during all three trimesters.[174,175] *[Evidence level 1+]*

It should be noted that a meta-analysis has shown that aspirin and/or LMWH does not increase the live birth rate in women with unexplained recurrent miscarriage, may be associated with adverse effects and should therefore not be used.[176] *[Evidence level 1+]*

7.2.2 | Inherited thrombophilias

Recommendation	Evidence quality`	Strength	Rationale for the recommendation
There is a lack of evidence to support routine treatment for women with Factor V Leiden, protein S deficiency and prothrombin gene mutation to reduce the incidence of recurrent miscarriage or second trimester loss.	2–	C	Subgroup meta-analysis of RCTs do not show a consistent benefit of treatment in women with inherited thrombophilia, however the subgroups were underpowered for firm conclusions.
A decision to treat women with recurrent miscarriage or second trimester loss can be individualised and should involve a discussion with the woman, taking into consideration additional risk factors, such as maternal risk of thrombosis (as described in RCOG Green-top Guideline No. 37a) or evidence of previous placental thrombosis.	3	D	Treatment can be considered given the association of thrombophilia with thrombotic events.

Thromboprophylaxis should be considered for women with inherited thrombophilias based on their risk of thrombosis.[177] Further prospective data are required to determine whether, or not, this would alter the risk of miscarriage and for which types, including heterozygous versus homozygous states. *[Evidence level 4]*

Meta-analyses of women with recurrent miscarriage combining women with and without thrombophilia have not shown any improvement in reproductive outcomes when using aspirin and/or heparin versus placebo.[176] Unfortunately, although the investigators planned

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to compare the thrombophilia versus no thrombophilia groups, they concluded that because of the lack of data, such an analysis was not possible. This means that the group of women with thrombophilias would have been underpowered in these analyses. *[Evidence level 2–]*

One prospective randomised trial demonstrated the efficacy of LMWH for the treatment of women with a history of a single late miscarriage after 10 weeks of gestation who have the Factor V Leiden or prothrombin gene mutation or have protein S deficiency. The live birth rate in women treated with enoxaparin was 86% compared with 29% in women taking low dose aspirin alone (OR 15.5, 95% CI 7–34).[178] In a later RCT, subgroup analysis of women with recurrent miscarriage with and without thrombophilia did not demonstrate a significant difference in live birth rate when comparing enoxaparin alone, enoxaparin/aspirin combined, and aspirin alone.[179] *[Evidence level 2–]*

Owing to the lack of data, thromboprophylaxis could be considered for women with Factor V Leiden, protein S deficiency and prothrombin G20210GA mutation, when there are risk factors for thrombosis (as per Green-top Guideline No. 37a *Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium*) and/or a history of second trimester miscarriage, particularly with evidence of placental thrombotic lesions.[180,181] Data of diagnosis and intervention should be collected for auditing or research purposes. *[Evidence level 3]*

7.3 | Genetic factors

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Options for couples with chromosomal rearrangements include attempting a further natural conception, PGT-SR or gamete donation.	**2–**	**C**	Live birth rates are similar following natural conception and PGD, and therefore PGD should not be routinely offered in this situation.
There are currently insufficient data to support the routine use of PGT-A for couples with unexplained recurrent miscarriage, while the treatment may carry a significant cost and potential risk.	**2–**	**C**	Observational studies have not demonstrated improved outcomes to date, both in terms of live birth rate and time to pregnancy interval. RCTs are urgently required.

Reproductive options in couples with chromosomal rearrangements includes proceeding to a further natural pregnancy, undergoing assisted reproductive treatment with preimplantation genetic testing for structural rearrangements (PGT-SR), formerly known as pre-implantation genetic diagnosis (PGD), or gamete donation.

Assisted reproduction (IVF/ICSI) combined with PGT-SR is gaining increased interest, with the aims of selecting embryos not affected by parental chromosomal rearrangement and proceeding with embryo transfer. A case–control trial involving 89 couples who underwent genetic counselling (of which 52 elected to attempt natural conception and 37 chose to undergo IVF/ICSI and PGD) demonstrated similar cumulative live birth rates (67.6% and 65.4%, respectively) between the two groups. The time to pregnancy was similar in both groups, however they reported a reduction in miscarriage rates with PGD and of course a significant financial burden of US$7956 per patient.[182] *[Evidence level 2–]*

A systematic review of non-RCTs reported similar live birth rates, time to conception rates and even miscarriage rates between natural conception and PGT-SR groups.[183] *[Evidence level 2–]*

Preimplantation genetic testing for aneuploidy (PGT-A), formerly known as preimplantation genetic screening (PGS), in conjunction with IVF/ICSI has also been advocated as a treatment option for women with recurrent unexplained miscarriage. Similar to the case of PGT-SR for parental chromosomal rearrangements, the rationale is that the identification and transfer of what are thought to be genetically normal embryos will lead to an increased likelihood of live birth.

A systematic review of non-RCTs found the live birth rates to be similar between expectant management groups and PGT-A groups, with a trend for lower miscarriage rates in the latter. However, it is worth noting that all studies performed embryo biopsy on day 3 of development.[184] *[Evidence level 2–]*

An intention to treat retrospective analysis involving 112 couples choosing PGT-A and 188 couples choosing expectant management found the pregnancy rate, miscarriage rate and live birth rate to be similar between the two groups. The median time to pregnancy was 6.5 months in the PGT-A group and 3.0 months in the expectant management group. Although the study is limited by its retrospective non-randomised nature, the embryo biopsies were performed on day 5 of development, which better reflects routine practice today.[185] *[Evidence level 2–]*

Overall, at present, couples should be informed of the risk and significant cost of undergoing PGT-SR and PGT-A, as well as the lack of evidence regarding any improvement in reproductive outcomes; for the latest updates couples can visit the HFEA website (www.hfea.gov.uk).

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7.4 | Anatomical factors

7.4.1 | Congenital uterine anomalies

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Resection of a uterine septum should be considered for women with recurrent first or second trimester miscarriage, ideally within an appropriate audit or research context.	**2+**	**C**	While there is a lack of RCTs dedicated to women with recurrent miscarriage, meta-analyses of observational studies have indicated that this treatment confers a significant benefit.

There are no published RCTs assessing the effectiveness and possible complications of hysteroscopic septum resection dedicated to women and people with recurrent miscarriage. There is, however, one RCT examining the effect of septum resection in women with a history of subfertility, pregnancy loss or preterm birth. It is worth noting that the initial ethical approval only included women with recurrent pregnancy loss (defined in the study as two or more miscarriages) but during the course of the trial, the eligibility criteria were extended to include women with a history of subfertility, one pregnancy loss or preterm birth. The trial found that hysteroscopic septum resection did not improve the reproductive outcomes of women with a septate uterus.[186]

Although this is the first RCT of its kind in the world, which deserves significant praise, a number of limitations have been highlighted. These include the broad inclusion criteria and the low number of subjects recruited (n = 80), despite the long duration of the trial (almost 8 years) and multiple participating sites (10 centres).[187] This may reflect the difficulty in recruiting patients to such a trial, as the only other RCT attempting to address this topic was stopped prematurely because of poor recruitment after recruiting only six patients (ISRCTN2896).[188]

When looking at systematic reviews and meta-analyses of observational studies, the latest publication in 2023, including 27 studies and 1506 patients, showed that hysteroscopic septum resection was associated with an increased live birth rate (RR 1.77, 95% Cl 1.26–2.49), reduced miscarriage rate (RR 0.36, 95% Cl 0.20–0.66) and reduced preterm birth rate (RR 0.15, 95% Cl 0.04–0.53).[189] *[Evidence level 2+]*

It is clear that further prospective RCTs are required to clarify the role of hysteroscopic resection in women with recurrent miscarriage. This is complicated not only by the potentially difficulty of recruiting patients, but also by the fact that the degree of fundal indentation that actually constitutes a septum remains to be determined. Therefore, for the time being, centres performing uterine septum resections are encouraged to do so within an appropriate audit or research context.

7.4.2 | Acquired uterine anomalies

Recommendation	Evidence quality	Strength	Rationale for the recommendation
There is a lack of evidence to guide the management of acquired uterine anomalies associated with recurrent miscarriage; counselling and the choice of expectant versus surgical options ought to be individualised.	**3**	**D**	There is a lack of studies examining relevant interventions.

There is limited evidence regarding both the association and treatment of acquired uterine anomalies in women and people with recurrent miscarriage. Data from one retrospective analysis in a recurrent miscarriage population with no control group suggests a potential benefit from the resection of submucosal myomas.[70] *[Evidence level 3]*

However, extrapolated data from the Cochrane review of women undergoing hysteroscopic myomectomy prior to assisted reproduction did not find a significant reduction in miscarriage rates compared with expectant management (OR 1.54, 95% CI 0.47–5.00; $P = 0.47$, 94 women; very low-quality evidence).[190] *[Evidence level 3]*

It is therefore clear that more prospective studies are urgently required.

7.4.3 | Cervical integrity

The treatment of suspected cervical insufficiency is covered in the NICE guideline [NG25] *Preterm labour and birth*.[191]

7.5 | Endocrine factors

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Thyroxine supplementation is not routinely recommended for euthyroid women with TPO who have a history of miscarriage.	**1–**	**A**	The 'TABLET' study, in which euthyroid women with TPO and a history of miscarriage were randomised to thyroxine or placebo, found no difference in live birth outcome. There were insufficient data to perform a subgroup analysis for women with recurrent miscarriage but the ongoing 'T4-Life' study (RCT) will examine this group.

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Thyroxine supplementation may be considered for women with moderate SCH (TSH more than 4 mIU/l) but is not routinely recommended for women with mild SCH (TSH more than 2.5 mIU/l) irrespective of TPO status.	**2+**	**B**	Based on the review of cohort studies and conclusion reached by the RCOG Scientific Impact Paper.
Regular TSH measurement from 7–9 weeks of gestation is recommended in cases with TPO and/or SCH.	**4**	**D**	Based on the review of cohort studies and conclusion reached by the RCOG Scientific Impact Paper No. 70.
Progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (for example 400 mg micronised vaginal progesterone twice daily at the time of bleeding until 16 weeks of gestation).	**1–**	**B**	The PRISM trial reported no significant differences in live births in women presenting with bleeding in early pregnancy and receiving progesterone supplementation; however, in the subgroup analysis of women with recurrent miscarriage, a significant improvement in live birth rate was observed.
Routine supplementation should be used with caution in asymptomatic women with unexplained recurrent miscarriage.	**1–**	**B**	Meta-analyses have reported a possible benefit from progestogen supplementation. However, there is a lack of consistently demonstrable benefit when used routinely in women with unexplained recurrent miscarriage, and there remains uncertainty about the optimal specific drug, route, timing and dose. The PROMISE trial, the largest multicentre RCT to date, which was adequately powered and with a very low risk of bias, showed that routine progesterone supplementation did not improve the outcome.

The TABLET study, which was a double-blind, placebo-controlled trial comparing live birth rates among euthyroid women with TPO antibodies and a history of miscarriage, treated with levothyroxine versus placebo, found no difference between the two groups, including subgroup analysis of women with recurrent miscarriage. However, there were insufficient data to perform a subgroup analysis of women with recurrent miscarriage, TPO antibodies and SCH.[192] However, the T4-LIFE study will hopefully shed some light on this exact question.[193] *[Evidence level 1–]*

In the context of SCH, for women at high risk (including women with previous miscarriages), the American Thyroid Association give a strong recommendation for thyroxine use with a TSH more than 4 mIU/l and autoimmunity, a weak recommendation for thyroxine with a TSH more than 2.5 mIU/l and autoimmunity and a weak recommendation for thyroxine in cases of TSH more than 4 mIU/l without autoimmunity.[150,151] This is consistent with findings of a meta-analysis.[76] *[Evidence level 2++]*

However, in terms of studies in the recurrent miscarriage population, the cohort study of Bernardi et al. (2013) in women with two or more miscarriages, found no statistically significant difference in the subsequent live birth rate when comparing women with SCH versus euthyroid women, or treated and untreated women with SCH.[85] Another observational trial has shown miscarriage rates to be similar in hypothyroid women receiving thyroxine and euthyroid women with TPO antibodies receiving thyroxine.[194] *[Evidence level 2–]*

On assessing the data available to date, RCOG Scientific Impact Paper No. 70 *Subclinical hypothyroidism and antithyroid autoantibodies in women with subfertility or recurrent pregnancy loss* concluded that there is low quality evidence for treatment of women with moderate SCH (TSH more than 4.0 mIU/l), but insufficient evidence to support treatment in mild SCH (TSH more than 2.5 mIU/l). They also recommended TSH measurement at 7–9 weeks of gestation and subsequent regular thyroid functions tests until 34 weeks of gestation. In cases of TPO euthyroid antibody status, they advise TSH measurement at 7–9 weeks of gestation and in each subsequent trimester because of the risk of progression to hypothyroidism.[149]

It should be mentioned that occult endocrinological anomalies (clinical hypothyroidism, thyrotoxicosis, diabetes, hyperprolactinaemia) should be treated in women with recurrent miscarriage as they would be treated preconceptionally for any woman or person. *[Evidence level 4]*

A systematic review and meta-analysis of ten RCTs of women with unexplained recurrent miscarriage receiving progesterone versus placebo or no treatment showed a lower risk of miscarriage (RR 0.72, 95% CI 0.53–0.97) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) respectively. No statistically significant differences were found in the other secondary outcomes, including preterm birth (RR 1.09, 95% CI 0.71–1.66), neonatal mortality (RR 1.80, 95% CI 0.44–7.34), and fetal genital anomalies (RR 1.68, 95% CI 0.22–12.62).[195] *[Evidence level 1+]*

A meta-analysis of the Cochrane collaboration in 2018 reported a reduction in the number of miscarriages for women given progestogen supplementation compared with placebo/controls (RR 0.69, 95% CI 0.51–0.92, 11 trials, 2359 women, moderate-quality evidence), with subgroup analysis showing

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a significantly more pronounced effect in women with three or more versus two or more prior miscarriages.[196] However, this analysis was updated the following year after the 2017 RCT by Ismail et al. became the subject of an investigation by the Journal of Maternal-Fetal & Neonatal Medicine and was eventually retracted because of concerns raised regarding the accuracy and reliability of the study data.[197] The updated meta-analysis concluded that there may still be a reduction in the number of miscarriages for women given progestogen supplementation compared with placebo/controls (RR 0.73, 95% CI 0.54–1.00, ten trials, 1684 women, moderate-quality evidence), while it is worth noting that on this occasion the 95% CI approached 1.00. A subgroup analysis on this occasion did not show significant differences between women with three or more versus two or more prior miscarriages.[198] *[Evidence level 1+]*

Caution should be exercised when interpreting the results of these meta-analyses due to differences in the RCTs included in the analyses.[199,200] For example, in the trial by Kumar et al. women were recruited at a mean gestational age of approximately 6.5 weeks and randomised after the confirmation of a live pregnancy with fetal heart activity to receive either oral dydrogesterone or placebo. Consequently, in their healthy control group a miscarriage rate of only 3.5% was observed, reflecting a potential selection bias.[200] In the PROMISE trial, 400 mg micronised vaginal progesterone twice daily was commenced as soon as there was a positive pregnancy test until 12 weeks of gestation.[201] Significant differences were observed in the former trial but not in the latter trial. *[Evidence level 1+]*

An RCT focusing on women with threatened miscarriage, the PRISM trial, compared the use of 400 mg micronised vaginal progesterone twice daily versus placebo at the time of bleeding until 16 weeks of gestation. The authors reported no significant differences in live births at more than 34 weeks (relative rate, 1.03, 95% CI 1.00–1.07; $P = 0.08$). However, on subgroup analysis of women with recurrent miscarriage, a significant improvement in live birth rate was observed (71.5% versus 57.4%; relative rate, 1.28, 95% CI 1.08–1.51; $P = 0.007$).[202] *[Evidence level 1–]*

A review and critical evaluation of the PROMISE and PRISM trials concluded that women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of progesterone.[19] *[Evidence level 1–]*

However, it is not yet clear which formulations, routes and timings of administration of progesterone may confer the most positive outcomes, and whether these factors may have an effect on the outcome of asymptomatic women and people with unexplained recurrent miscarriage. Future trials should aim to address these questions and control for aneuploid pregnancy losses were possible, as these miscarriages cannot be avoided with progesterone supplementation.

7.6 | Immune factors

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Immunotherapy (e.g. paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin [IVIg]) is not recommended for women with recurrent miscarriage.	**1++**	**B**	Meta-analyses have shown no significant benefit of treatment.

A Cochrane systematic review and meta-analysis has shown that the use of various forms of immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and IVIg, in women with unexplained recurrent miscarriage provides no significant beneficial effect over placebo in preventing further miscarriage.[203] Moreover, immunotherapy is expensive and has potentially serious adverse effects including transfusion reaction, anaphylactic shock and hepatitis. The use of immunotherapy should no longer be offered to women with unexplained recurrent miscarriage. *[Evidence level 1++]*

There are no published data on the use of anti-tumour necrosis factor (TNF) agents to improve pregnancy outcome in women with recurrent miscarriage. Further, anti-TNF agents could potentially cause serious morbidity including lymphoma, granulomatous disease such as tuberculosis, demyelinating disease, congestive heart failure and syndromes similar to systemic lupus erythematosus.[204]

Immune treatments should not be offered routinely to women with recurrent miscarriage outside formal research studies.

7.7 | Male factors

Recommendation	Evidence quality	Strength	Rationale for the recommendation
There is no evidence to recommend treatments for male factors.	**3**	**D**	There is a lack of studies examining relevant interventions.

To date, there is a paucity of studies available evaluating interventions that may improve the outcome of couples with recurrent miscarriage, in particular through reducing sperm DNA fragmentation, which has been implicated

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in miscarriage. Such interventions could include lifestyle modifications (i.e. smoking cessation, weight loss/exercise, reduction in pollutant exposure), treatment of infections, control of diabetes, treatment of varicocele, antioxidant therapy, sperm selection and others.[132] *[Evidence level 3]*

7.8 | Unexplained recurrent miscarriage

7.8.1 | Endometrial scratch

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Endometrial scratch is not recommended in women with recurrent miscarriage.	**2++**	**C**	There are no studies available for women with recurrent miscarriage but no benefit in miscarriage reduction has been shown within the infertility context.

Endometrial scratch or injury has been researched extensively in the context of IVF/ICSI with a suggestion that it may improve the clinical pregnancy rates, although to date RCTs and meta-analyses in this patient group have failed to show a reduction in miscarriage rates.[205,206] *[Evidence level 2++]*

A Cochrane review assessing women undergoing endometrial scratch/injury prior to intrauterine insemination or sexual intercourse found no evidence of a difference in miscarriage rate per clinical pregnancy (RR 0.73, 95% CI 0.38–1.39; six RCTs, 174 participants; I^2 statistic = 0%;).[207] *[Evidence level 2++]*

There is no evidence regarding women with recurrent miscarriage and therefore by extrapolation of the data above endometrial scratch should not be recommended for women and people with unexplained recurrent miscarriage.

7.8.2 | Psychological support

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with unexplained recurrent miscarriage should be offered supportive care, ideally in the setting of a dedicated recurrent miscarriage clinic.	**2+**	**C**	Several observational studies have suggested a beneficial effect in pregnancy outcomes.

A significant proportion of cases of recurrent miscarriage remain unexplained, despite detailed investigation. These women and their partners can be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%.[20,21] However, the prognosis worsens with increasing maternal age and the number of previous miscarriages. The value of psychological support in improving pregnancy outcome has not been tested in the form of an RCT. However, data from several non-randomised studies have suggested that attendance at a dedicated early pregnancy clinic has a beneficial effect,[20,21,208,209] although it has been recognised that a significant proportion of women with unexplained recurrent miscarriage may be healthy women with repeated sporadic miscarriages and no persisting pathology.[2,7] *[Evidence level 2+]*

Further research is required to develop appropriate screening and management approaches for women and couples with mental health illness, as an association of miscarriage with anxiety, depression, post-traumatic stress disorder, and suicide has been shown.[11]

8 | MANAGEMENT OF SUBSEQUENT MISCARRIAGES

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Provisions should be made for women and people to receive appropriate supportive care in terms of communication with healthcare professionals, ultrasound examinations and access to services in case of subsequent miscarriage(s).	**3**	**D**	It will enable appropriate psychological support, prompt diagnosis and may facilitate the investigation of the miscarriage, which may help with counselling and future management.

A proportion of women will experience further miscarriage(s) following referral. Provisions should be made to allow them to contact or access services,[210] particularly if there have been plans in place regarding the management of possible future miscarriage, such as collection of pregnancy tissue for cytogenetic analyses. This can be organised for spontaneously miscarried pregnancies or those undergoing manual vacuum aspiration or surgical management of miscarriage. *[Evidence level 4]*

A questionnaire study in women with recurrent miscarriage reported that women preferred the following supportive care options for their next pregnancy:

- A plan with one doctor who shows understanding, takes them seriously, has knowledge of their obstetric history, listens to them, gives information about recurrent miscarriage, shows empathy, informs on progress and enquires about emotional needs.
- An ultrasound examination during symptoms, directly after a positive pregnancy test and every 2 weeks.
- If a miscarriage occurred, most women would prefer to talk to a medical or psychological professional afterwards.

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- The majority of women expressed a low preference for admission to a hospital ward at the same gestational age as previous miscarriages and a low preference for bereavement therapy.

Ethnicity, parity and pregnancy at the time of the survey were associated with different preferences, but female age, education level and time passed since the last miscarriage were not.[211]

9 | RECOMMENDATIONS FOR FUTURE RESEARCH

- Establishing the causes for increased incidence of miscarriage in women of a Black ethnic background and development of appropriate management strategies.
- Value of genetic testing of the pregnancy tissue after two versus three miscarriages.
- Prognostic value of genital tract microbiome and associated antibiotic therapy on clinical outcomes.
- Association and treatment of anti-beta-2-glycoprotein-1 antibodies in recurrent miscarriage.
- Impact of inherited thrombophilia and its treatment on clinical outcomes.
- Impact of resection versus expectant management of uterine septum on clinical outcomes.
- Impact of acquired uterine anomalies and their treatment on clinical outcome.
- Impact of TPO antibodies and treatment with levothyroxine on clinical outcomes.
- Impact of different formulations, routes and timings of administration of progesterone on clinical outcomes.
- Comparison of different techniques for collecting pregnancy tissue.
- Comparison of different techniques for analysing pregnancy tissue.
- Prognostic value of sperm DNA fragmentation and impact of treatment interventions on clinical outcome.
- Impact of PGT-SR in couples with chromosomal rearrangements on clinical outcome.
- Impact of PGT-A in couples with chromosomal rearrangements on clinical outcome.
- Development of screening and management approaches for women with mental health illness after recurrent miscarriage.

10 | AUDITABLE TOPICS

- Percentage of women and people completing the recommended investigations (100%).
- Percentage of women and people with successful cytogenetic analysis of pregnancy tissue when attempted (more than 90%).
- Percentage of women and people with pregnancy outcome recorded (100%).

11 | USEFUL LINKS AND SUPPORT GROUPS

- Miscarriage Association: https://www.miscarriageassociation.org.uk/
- Tommy's: https://www.tommys.org/

CONFLICT OF INTERESTS

LR reports royalties from a book publication. SS has declared no conflicts of interest. RR has declared no conflicts of interest. TCL has declared no conflicts of interest. Full disclosures of interest for the developers, Guidelines Committee and peer reviewers are available to view online as supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

✓	Recommended best practice based on the clinical experience of the guideline development group

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APPENDIX 2

Association between various factors and the risk of miscarriage

Factor	Description	Estimate measure	Point estimate + CI (where available)	Evidence level
Epidemiological				
Maternal age[a]	12–19 years[3,a]	OR	1.22 (1.19–1.25)	2++
	20–24 years[3,a]	OR	1	2++
	25–29 years[3,a]	OR	1.08 (1.06–1.09)	2++
	30–34 years[3,a]	OR	1.40 (1.38–1.43)	2++
	35–40 years[3,a]	OR	2.52 (2.46–2.57)	2++
	≥40–44 years[3,a]	OR	7.08 (6.80–7.37)	2++
	≥45 years[3,a]	OR	30.38 (25.66–35.97)	2++
Paternal age[a]	25–29 years[18,a]	OR	1	2++
	30–34 years[18,a]	OR	1.04 (0.90–1.21)	2++
	35–39 years[18,a]	OR	1.15 (0.92–1.43)	2++
	40–44 years[18,a]	OR	1.23 (1.06–1.43)	2++
	≥45 years[18,a]	OR	1.43 (1.13–1.81)	2++
Number of previous miscarriages	None[3,a]	OR	1	2++
	1[19,a]	OR	1.61 (1.57–1.64)	2++
	2 or 3[19,b]	OR	3.05 (2.95–3.16)	2++
	4[19,b]	OR	5.15 (4.72–5.62)	2++
	5[19,b]	OR	7.02 (6.11–8.08)	2++
	6[19,b]	OR	13.84 (11.00–17.41)	2++
Race	White European[22,a]	aOR	1	2+
	Black African[22,a]	aOR	1.20 (1.12–1.29)	2+
	Black Caribbean[22,a]	aOR	1.31 (1.21–1.41)	2+
Lifestyle	Smoking[25,a]	OR	1.20 (1.04–1.39)	2+
	Caffeine low intake (50–149 mg/day)[27,a]	RR	1.02 (0.85–1.24)	2++
	Caffeine moderate intake (150–349 mg/day)[27,a]	RR	1.16 (0.94–1.41)	2++
	Caffeine high intake (350–699 mg/day)[27,a]	RR	1.40 (1.16–1.68)	2++
	BMI < 19 kg/m[2][31,b]	OR	1.2 (1.12–1.28)	2++
	BMI > 25 kg/m[2][31,b]	OR	1.21 (1.06–1.38)	2++
	Alcohol[26,a]	aHR	3.7 (2.0–6.8)	2+
Thrombophilia				
Acquired	Lupus anticoagulant[b]	OR	7.79 (2.30–26.4)	2++
	IgM cardiolipin[b]	OR	5.61 (1.26–25.03)	2++
	IgG cardiolipin[b]	OR	3.57 (2.26–5.65)	2++
	Anti-beta-2-glycoprotein-I[b]	OR	*2.12 (0.69–6.53)*	2++
Inherited	Factor V Leiden[b]	OR	1st trimester: 2.01 (1.13–3.58) 2nd trimester: 7.83 (2.83–21.67)	2++
	Prothrombin gene mutation[b]	OR	1.81 (1.26–2.60)	2++
	Protein S deficiency[b]	OR	*14.72 (0.99–218.1)*	2++
Genetic				
	Parental chromosome rearrangements[49,b]	OR	2.22 (1.60–3.08)	2+
	Previous euploid miscarriage[57,b]	OR	2.62 (1.29–5.32)	2+

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Anomalies				
Congenital	All anomalies[62,b]	RR	1.13 (1.06–1.22)	2++
	Arcuate[62,a]	RR	*1st trimester: 1.22 (0.87–1.72) 2nd trimester: 1.98 (1.06–3.69)	2++
	Septate[62,a]	RR	1st trimester: 2.65 (1.39–5.06) 2nd trimester: 2.95 (1.51–5.77)	2++
	Bicornuate[62,a]	RR	1st trimester: 2.32 (1.05–5.13) 2nd trimester: 2.90 (1.56–5.41)	2++
	Didelphis[62,a]	RR	*1st trimester: 1.13 (0.45–2.86) *2nd trimester: 1.71 (0.63–4.59)	2++
	Unicornate[62,a]	RR	*1st trimester: 1.38 (0.83–2.28) *2nd trimester: 2.27 (0.64–7.96)	2++
Acquired	Fibroids[67,a]	RR	*1.16 (0.80–1.52)	3
Endocrine	Thyroid autoantibodies[88,b]	OR	1.86 (1.18–2.94)	2++
Male	Sperm DNA fragmentation[127,a]	RR	2.28 (1.55–3.35)	2++

[a]Data from general population

[b]Data from recurrent miscarriage population

*Not reaching statistical significance

Reference groups have an OR of 1

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APPENDIX 3

Techniques for genetic analysis of pregnancy tissue

CONVENTIONAL KARYOTYPING

Conventional karyotyping is limited by culture failure, with pooled rates of approximately 20% (756/3859) and maternal cell contamination rates of approximately 22% (269/1222) according to one study.[53,212]

Recommendations to avoid these issues have included: i) to obtain and dispatch to the cytogenetic lab the pregnancy tissue as soon possible following the diagnosis of a miscarriage (to avoid culture failure); ii) to gently wash the tissue with normal saline (to reduce maternal blood contamination); and iii) to store the remaining part of the specimen at −80°C if traditional karyotyping is performed (to allow for the option of fluorescence in situ hybridisation [FISH] or molecular genetic testing in the case of culture failure).[53]

FLUORESCENCE IN SITU HYBRIDISATION (FISH)

FISH uses fluorescent probes that bind to specific parts of a chromosome and is therefore limited to the specific probes utilised (e.g. 13, 16, 18, 21, 22, X, and Y).[213] Using this technique, up to 97% of culture failures have been shown to yield results,[214] with chromosomal anomalies eventually detected in up to 53% of them.[215]

ARRAY COMPARATIVE GENOMIC HYBRIDIZATION (CGH)

Array CGH is a form of chromosomal microarray analysis based on the use of differentially labelled test and reference genomic DNA samples that are simultaneously hybridised to DNA targets arrayed on a glass slide or other solid platform.[216] It avoids the limitations of conventional karyotyping and FISH, such as culture failure and limited chromosome examination, and essentially scans the entire genome providing additional information such as DNA copy number variants. In the standard clinical setting most recent studies report virtually no failure rate in diagnosis.[217]

SINGLE NUCLEOTIDE POLYMORPHISM (SNP)

SNP array is a form of chromosomal microarray analysis similar to array CGH. It can additionally detect the parental source of chromosomes and anomalies and can therefore be used to rule out maternal cell contamination.[212]

NEXT GENERATION SEQUENCING (NGS)

NGS achieves single nucleotide resolution through a high-throughput platform. Its advantage is that it can scrutinise the entire genome through a tiny quantity of tissue. Its disadvantage is that it is currently expensive and requires data processing steps and bioinformatics because of its large data output.[53]

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The following organisations and individuals submitted comments at peer review:

A Aggarwal FRCOG, Leeds; A Ali MRCOG MRCPI, Epsom; D D'Costa MRCOG, Prescot; MJ Ekanayake FRCOG, Chelmsford; Fair Treatment for the Women of Wales; M Fawzy FRCOG, Barnsley; R Ganapathy MD FRCOG, Epsom; S Gordon FRCS(Urol), Sutton; A Gorry MRCOG, London; H Jan MRCOG, Epsom; RU Khan FRCOG, London; A Mighell MRCOG, Bradford; RF Neilson FRCP, FRCPath, Forth Valley Royal Hospital, Larbert; S Quenby FRCOG, Warwick; Royal College of Nursing; JA Ross FRCOG, London; HAH Shehata FRCOG FRCPI, Epsom; RK Viswanatha FRCOG, Croydon; W Vlaanderen, Nijmegen, The Netherlands; and R Wilding RN, CRADLE Charity.

Committee lead reviewers were: Miss NP Potdar FRCOG, Leicester[1]; Dr R Davies MRCOG, Stoke[2]; and Dr M Annappa FRCOG, Lincolnshire[2].

[1]from June 2020; [2]until May 2021.

The chairs of the Guidelines Committee were: Mr A McKelvey MRCOG, Norwich[1]; Miss NP Potdar FRCOG, Leicester[1]; Dr MA Ledingham MRCOG, Glasgow[2]; and Dr B Magowan FRCOG, Melrose[2].

[1]co-chairs from June 2021; [2]until May 2021.

The final version is the responsibility of the Guidelines Committee of the RCOG.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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