# Recurrent pregnancy loss: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Washington, D.C.

Current strategies for the assessment and treatment of recurrent pregnancy loss are discussed. This replaces the previous document, titled, "Evaluation and treatment of recurrent pregnancy loss: a committee opinion," last published in 2012. (Fertil Steril® 2026;■: ■–■. ©2026 by American Society for Reproductive Medicine.)

**Key Words:** Recurrent pregnancy loss, miscarriage, female fertility, male fertility, genetics

The American Society for Reproductive Medicine (ASRM) defines recurrent pregnancy loss (RPL) as the spontaneous loss of two or more pregnancies, excluding confirmed molar or ectopic pregnancies. Pregnancies confirmed by urinary or blood human chorionic gonadotropin (HCG) are sufficient. Ultrasound or tissue confirmation is not required, as access to early pregnancy ultrasound and care is variable across patient populations. In addition, it has been established that biochemical pregnancy losses confer a similar impact on recurrence risk as clinical losses, supporting the inclusion of biochemical pregnancy losses in the definition of RPL (1–3). Recurrent pregnancy loss is a disease distinct from infertility, requiring its own specific evaluation and management. There are inconsistent definitions of miscarriage (or spontaneous abortion) in the literature to define pregnancy losses as less than 20 or 22 weeks. For the purpose of this document, we will use less than 22 weeks, which is consistent with the International Glossary of Infertility and Fertility Care (4). Pregnancy loss after 22 weeks is considered a stillbirth or fetal demise and is outside the scope of this document and covered by a dedicated American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine consensus guideline (5, 6).

Approximately 50%–60% of first-trimester miscarriages are due to embryonic aneuploidy (7). Sporadic aneuploidy is strongly correlated with maternal age. Aneuploidy plays a smaller role in second and third trimester losses and stillbirths, impacting 20% of stillborn fetuses at 22 weeks of gestation, 6% of stillborn infants at term, and 0.1%–5% of term live births (8). When compared with individuals with isolated miscarriage, patients with RPL have a higher likelihood of euploid miscarriage. The likelihood of euploid miscarriage further increases with the number of miscarriages. Large observational cohort studies show that women with RPL have an elevated risk of several serious health conditions later in life, including cardiovascular disease, stroke, diabetes, autoimmune disorders, and mental health disorders (9). Therefore, a complete evaluation of maternal and paternal health is essential in the setting of recurrent miscarriage, especially if $\geq 1$ miscarriages are found to be euploid, termed "unexplained". The definition of RPL does not require miscarriages to be consecutive, due to a lack of definitive associations with consecutive miscarriages and known risk factors for RPL. However, clinicians are urged to use their judgment on when to initiate a partial or complete workup in the setting of nonconsecutive miscarriages, as limited data indicate that consecutive miscarriages have a poorer prognosis for live birth than nonconsecutive miscarriages in one observational cohort (10). Management of this traumatic diagnosis drives patients and providers to seek answers and attempt unproven therapies. However, counseling about the natural history of RPL is a key component and responsibility of the provider, as 50%–80% of patients will succeed in their subsequent pregnancy attempt with no specific interventions (11, 12). Although ASRM supports shared decision-making in the absence of high-quality data, taking care of patients with this multifactorial disorder should include an evidence-based approach in a supportive environment to minimize risks of harm because of unproven treatments.

In this document, we present a stepwise algorithm for the evaluation of RPL, with the recommendation to perform chromosome evaluation of the miscarriage, followed by additional testing as indicated (see Fig. 1, Table 1, and Table 2). The incremental benefit of adding miscarriage testing to the diagnostic workup of patients with recurrent miscarriage has been demonstrated in numerous studies (13–15).

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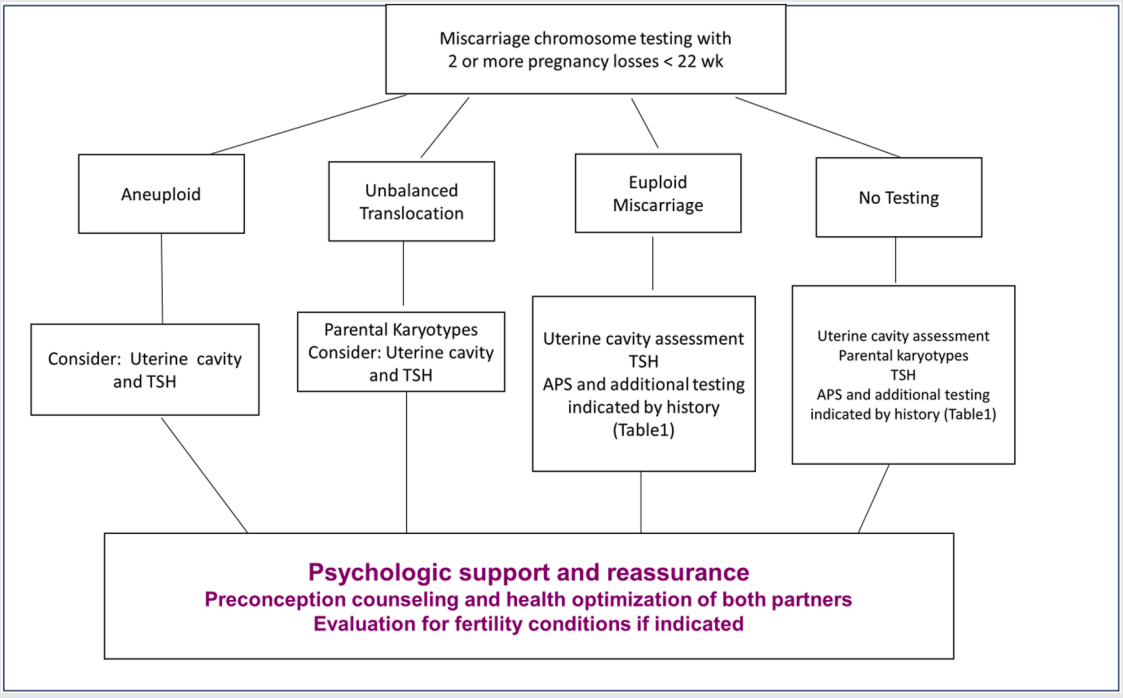
**FIGURE 1**




Approach to recurrent pregnancy loss on the basis of chromosome testing of the most recent miscarriage. APS = antiphospholipid syndrome.

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Therefore, we propose a stepwise algorithm, which provides more explanations and substantial cost savings by avoiding unnecessary testing when miscarriages are explained. Although chromosome testing at the time of first miscarriage can be offered for explanatory purposes, a single euploid early miscarriage has not been shown to increase the risk of second loss (16); therefore, reflex testing for other causes of losses is not indicated after a single euploid miscarriage.

## GENETIC EVALUATION OF MISCARRIAGE

The ASRM, European Society of Human Reproduction and Embryology (ESHRE), ACOG, and Royal College of Obstetricians and Gynaecologists (RCOG) have all suggested considering the genetic analysis of the miscarriage tissue in the evaluation of RPL for explanatory purposes and/or psychological benefit to patients (17–20). Given new data on cost-effectiveness, patient satisfaction, and emotional benefits, ASRM now recommends offering a genetic evaluation of miscarriage tissue to all patients experiencing their second miscarriage or with a history of recurrent miscarriage. Whole chromosome aneuploidy is the most commonly identified cause of sporadic and recurrent miscarriage (12, 21). The rate of aneuploidy is strongly correlated with maternal age and has been demonstrated in approximately 50% of miscarriages tested in young women (<35 years) and in 75% of miscarriages in women over 40 (22). Chromosome testing of miscarriage is highly desired by patients (23), as testing provides a psychological benefit by reducing feelings of guilt and self-blame. In addition, chromosome testing at the time of a second miscarriage has been shown to frequently provide an explanation (15) and reduce cost in the setting of RPL (13, 24). Chromosomal abnormalities account for the majority of first-trimester miscarriages, most of which are sporadic and nonrecurrent. Detecting the etiology of a miscarriage, especially if it is found to be a sporadic aneuploid event, can allow for the avoidance of an expensive RPL workup, guide counseling, and alleviate a couple's anxiety and sense of guilt. Although surgical management of miscarriage is most likely to provide optimal material testing, at-home collection kits are available and can be successful after medical management (25). For many years, conventional metaphase G-banding karyotyping was the standard technique to evaluate miscarriage tissue for aneuploidy. However, this technique has significant limitations, including high rates of cell culture failure (10%–40%), maternal cell contamination (contributing to high rates of false negative results), inability to process samples already placed in formalin, and inability to detect microdeletions and microduplications <5 Mb (26–31).

Fluorescence in situ hybridization (FISH) has its own advantages, but it also has significant disadvantages (time-consuming, probe-design dependent sensitivity, targeting only specific chromosomes) that limit its successful applicability to the diagnosis of common numeric chromosome abnormalities (18, 32).

## TABLE 1

**Testing in couples/ individuals identified with recurrent pregnancy loss.**

| Evaluation | Indication | Test |
|---|---|---|
| Recommended | | |
| Chromosome evaluation of miscarriage tissue | All patients | Array-based chromosome testing |
| Uterine cavity evaluation | All patients | HSG, saline sonogram, or hysteroscopy |
| Recommended in certain circumstances | | |
| Parental karyotypes | Miscarriage with unbalanced translocation or no miscarriage testing | Blood karyotype of male and female |
| Antiphospholipid antibodies | Clinical criteria for antiphospholipid syndrome (APS)<br>- 3 or more consecutive losses<br>- personal history of thrombosis | Anticardiolipin IgG and IgM<br>Beta-2-glycoprotein IgG and IgM<br>Lupus anticoagulant |
| Thyroid | Risk factors or symptoms, Euploid miscarriage, or no miscarriage testing | TSH |
| Chronic endometritis | Recurrent unexplained miscarriage or concurrent infertility | Endometrial biopsy with CD138 staining |
| Sperm DNA fragmentation testing | Recurrent unexplained miscarriage or concurrent infertility | Sperm DNA fragmentation<br>Reproductive urology evaluation |
| Diabetes | Risk factors or symptoms (PCOS, obesity, age >40) | HgbA1c |
| Prolactin | Symptoms of hyperprolactinemia (anovulation, galactorrhea) | Fasting prolactin |
| Not recommended | | |
| Inherited thrombophilia | Not recommended | Factor V Leiden, Prothrombin gene, MTHFR, protein C, protein S, antithrombin 3, homocysteine |
| Autoimmune testing outside of APS | Not recommended | Thyroid antibodies<br>NK cell testing |
| Endometrial receptivity testing | Not recommended | |
| Microbiome testing (including mycoplasma and ureaplasma) | Not recommended | |

*Note:* APS = antiphospholipid syndrome; DNA = deoxyribonucleic acid; HSG = hysterosalpingography; IgG = immunoglobulin G; IgM = immunoglobulin M; MTHFR = methylenetetrahydrofolate reductase; NK = natural killer; PCOS = polycystic ovary syndrome; TSH = thyroid-stimulating hormone.

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Molecular karyotyping by array comparative genomic hybridization (aCGH), next-generation sequencing (NGS), and single-nucleotide polymorphism (SNP) based microarrays have distinct advantages over conventional cytogenetics. With these techniques, there is no need for cell culture, a fast turnaround time, and the ability to use archived miscarriage tissue or home-collected tissue (30, 33, 34). Additionally, these techniques allow detection of microduplications and microdeletions that would otherwise be missed by conventional karyotyping.

Maternal cell contamination of miscarriage tissue is a common problem in miscarriage analysis and limits the interpretation of 46,XX results. The maternal cell contamination rate is highly provider-dependent and can be minimized by careful tissue sampling and cleaning (35, 36). Molecular fingerprinting can be completed as an adjunct to most methodologies to compare maternal and miscarriage deoxyribonucleic acid (DNA) using highly polymorphic markers, such as SNPs.

Any technology that detects whole chromosome abnormalities will identify the most common aneuploidies in first-trimester miscarriage. However, each platform has advantages and limitations. Conventional metaphase karyotyping can detect mosaicism and balanced chromosomal rearrangements. The SNP-based microarrays provide information on uniparental disomy and consanguinity, offer decreased cost, rule out maternal cell contamination, and have the ability to identify the parent of origin for the aneuploidy. Although aCGH cannot detect balanced translocations, SNP cannot detect balanced tetraploidy. Next-generation sequencing can detect segmental aneuploidy and mosaicism. Emerging evidence has confirmed the accuracy and efficiency of NGS testing in the miscarriage tissue evaluation (37). No single technique can detect all possible genetic abnormalities, and the most comprehensive results might be obtained by combining different techniques.

## Summary statement

- *The ASRM recommends chromosome analysis of miscarriage tissue, when feasible, as a first step in the evaluation of the couple with RPL. The American Society for Reproductive Medicine joins ESHRE and ACOG in recommending array-based technology for analysis of miscarriage tissue on the basis of its many technical advantages over traditional cytogenetic analysis. Options for at-home collection of tissue for miscarriage tissue testing should be discussed with patients at the time of miscarriage for patients who do not desire surgical management.*

## UTERINE CAVITY EVALUATION

Given the risk of retained pregnancy tissue, intrauterine adhesions, and the increased prevalence of anatomic abnormalities among patients with RPL (38–40), an evaluation of the uterine anatomy should be offered to all women with RPL (17–19,41).

### Congenital uterine anomalies

The higher prevalence of congenital uterine anomalies among women with RPL is well established. Congenital uterine anomalies are detected more often among these women compared with the general population [risk ratio [RR] (95% confidence interval [CI]): 13.3% (8.9–20) vs. 5.5% (3.5–8.5)], and prevalence does not appear to differ substantially with two vs. three miscarriages (18, 38, 39). In a meta-analysis, the probability of miscarriage was higher [RR (95%CI): 1.68 (1.31–2.15)] among women with congenital uterine anomalies compared with controls. Additionally, septate and bicornuate uteri were associated with an increased probability of first- and second-trimester miscarriage; for septate [RR (95%CI): 2.65 (1.39–5.09), and 2.95 (1.51–5.77) and bicornuate uteri 2.32 (1.05–5.13)] and 2.90 (1.56–5.41), respectively (40).

A variety of noninvasive or minimally invasive diagnostic procedures are currently available to accurately evaluate uterine anatomy and pathology, including hysterosalpingography (HSG), 2- and 3-dimensional ultrasonography, hysterosalpingo contrast sonography (HyCoSy), sonohysterography (SHG), hysteroscopy, magnetic resonance imaging (MRI), and laparoscopy. Each diagnostic technique has distinct advantages and disadvantages, and each one can be used in combination with another, as needed, in complex diagnostic cases. Overall, techniques that permit accurate evaluation of the uterine contour (outer and inner) are more informative in the detection and accurate classification of congenital uterine anomalies (42). The sensitivity and specificity of SHG in diagnosing uterine malformations are higher than those of either HSG or diagnostic hysteroscopy (43). Additionally, its combination with 3-dimensional ultrasonography allows for the visualization of the inner and outer uterine contour, further increasing its sensitivity and specificity.

The Thessaloniki ESHRE/European Society for Gynaecological Endoscopy (ESGE) consensus on diagnosis of female genital anomalies reported on the overall diagnostic accuracy of available diagnostic technologies and concluded that 3-dimensional ultrasonography had the highest accuracy (97.6%), followed by SHG (96.5%), 2-dimensional ultrasound (86.6%), and HSG (86.9%). Moreover, MRI correctly subclassified 85.8% of anomalies, accurately diagnosing congenital uterine malformations in well over 90% of the cases (41). An advantage of MRI is that it often permits the concurrent diagnosis of urinary tract abnormalities (often coexisting with Müllerian duct anomalies); however, its high cost precludes its use as a first-line diagnostic modality. The new ASRM Müllerian anomalies classification is an excellent tool for guiding the identification, diagnosis, and treatment of these anomalies (42).

**Treatment of congenital uterine malformations.** Hysteroscopic metroplasty is the most common procedure for septum resection and is considered safe and effective by this minimally invasive approach. Although associations exist between congenital and acquired abnormalities and poor pregnancy outcomes, data supporting a clear positive impact of surgical management remain limited. For example, untreated Müllerian anomalies were associated with lower implantation rates and higher miscarriage risk in a large series of donor egg cycles. Treatment of anomalies did appear to provide some benefit but did not normalize miscarriage risk (44). Additionally, a retrospective cohort of 257 women with a range of reproductive presentations demonstrated no difference in livebirth or miscarriage rate after septum resection and a smaller study of 32 recurrent early pregnancy loss patients in the US similarly showed no improvement in live birth or miscarriage. A meta-analysis of 10 observational studies of all comers showed a reduction in miscarriage and malpresentation but no difference in live birth after hysteroscopic metroplasty (45–51). Although not designed to specifically assess a role for septum resection in RPL, a multicenter, international randomized controlled trial (RCT) comparing septum resection vs. no resection in women with a history of subfertility, one prior early miscarriage or history of preterm birth and a documented uterine septum did not find an improvement in live birth rate (LBR) with septum resection (31%) compared with expectant management (35%) (RR 0.88, 95% CI 0.47 to 1.65) (52). However, this RCT had significant limitations, including a small sample size, a heterogeneous study population, a lack of standardized surgical approach (electrosurgical and/or mechanical), and a short follow-up period for the outcome of live birth (45–48). According to the ASRM uterine septum guideline, it is recommended to offer hysteroscopic septum incision to patients with a septum and RPL in a shared decision-making model (53). In contrast, no clear evidence supports the surgical correction of arcuate, bicornuate, unicornuate uterus (54).

### Acquired intracavitary pathology

The role of acquired intracavitary pathology (i.e., endometrial polyps, submucosal fibroids, intrauterine adhesions [IUA]) in RPL is unclear. The prevalence of endometrial polyps, fibroids, and IUA in RPL varies, depending on the study (1.6%–6%, 0.5%–1.3%, and 1.3%–9.6%, respectively) (54, 55). Hysteroscopy can easily and accurately diagnose such intrauterine anomalies, whereas SHG can aid by delineating submucosal myomas and permitting the evaluation of their proximity to the endometrial cavity in case of intramural myomas, all with high accuracy.

**Treatment of acquired uterine malformations.** The benefit of surgical intervention for acquired anomalies is still controversial, as high-quality, randomized studies are lacking that conclude a reduction in the risk of miscarriage. Nevertheless, in clinical practice, endometrial polyps, submucosal myomas, and IUAs are the primary reasons for surgical intervention in the management of RPL (54).

Hysteroscopic myomectomy for the treatment of submucosal fibroids can improve the chance of pregnancy. However, the data are unclear whether there is a benefit of surgery

**TABLE 2**

**Treating couples/individuals identified with recurrent pregnancy loss.**

| | |
|---|---|
| Standard recommended treatments | Preconception optimization of maternal health conditions (such as lupus, hypertension)<br>Psychological support<br>Treatment of APS with heparin and low-dose aspirin<br>Treatment of overt thyroid disease<br>Treatment of uncontrolled Diabetes Mellitus<br>Genetic counseling in a setting of known genetic cause (parental translocation) or high-risk family history<br>Treatment of hyperprolactinemia |
| Treatments of possible benefit, with limited or conflicting studies | Correction of uterine cavity abnormalities (uterine septum, polyps, submucosal fibroids, intrauterine adhesions)<br>Addition of progesterone support if the patient has bleeding in the first trimester<br>Empiric use of progesterone in the luteal phase<br>Treatment of chronic endometritis<br>Reproductive Urology evaluation if elevated sperm DNA fragmentation<br>Use of Metformin for women with PCOS or evidence of insulin resistance<br>IVF for PGT-A or PGT-SR<br>Use of donor gametes in a setting of genetic cause found or advanced maternal age with diminished ovarian reserve |
| Treatments proven ineffective or no evidence of benefit | Use of empiric aspirin and thrombolytics in the absence of positive APS testing<br>Treatment of endometriosis and adenomyosis<br>Treatment of hyperprolactinemia in the absence of ovulatory disorder<br>Treatment of inherited thrombophilia<br>Thyroid hormone supplementation in patients with isolated TPO antibodies or TSH less than 4 mIU/L<br>IVIG, intralipids, or prednisone |

*Note:* APS = antiphospholipid syndrome; DNA = deoxyribonucleic acid; IVIG = intravenous immunoglobulin; IVF = in vitro fertilization; PCOS = polycystic ovary syndrome; PGT-A = preimplantation genetic testing for aneuploidy; PGT-SR = preimplantation genetic testing for structural rearrangements; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

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in terms of reduction in miscarriage within an RPL population (47). For intramural fibroids without cavity involvement, a clear benefit of removal has not been shown (47). For multiple fibroids, as well as submucosal fibroids with a significant intramural component, an abdominal approach to myomectomy can be considered, including a laparoscopic approach when appropriate (54). Despite the lack of high-quality data, observational studies support hysteroscopic myomectomy as a treatment for submucosal fibroids in couples with RPL. The ASRM suggests removing large cavity deforming fibroids or those directly impacting the cavity (submucosal or a submucosal component) to improve pregnancy rates (47, 56).

Universally accepted recommendations do not exist to guide the management of endometrial polyps. A review of studies on fertility outcomes after hysteroscopic polypectomy remains too limited for universal recommendation within the RPL population. Hysteroscopic polypectomy is overall widely regarded as a safe procedure with a very low complication rate (57). Case reports have suggested an improvement in LBR when hysteroscopic polypectomy is utilized before intrauterine insemination cycles (58, 59). However, the data within the in vitro fertilization (IVF) population remains conflicting (18, 19, 58). Given that limited data demonstrate an increase in live birth in infertile women after polypectomy, it is reasonable to consider offering hysteroscopic polypectomy for women with RPL found to have endometrial polyps. Lastly, plasma cells, a key feature of chronic endometritis, are often encountered in association with polyps; however, polypectomy is likely sufficient for treatment rather than antibiotics (60, 61).

Recurrent pregnancy loss is an independent risk factor for the development of intrauterine adhesions. Intrauterine adhesions, also referred to as Asherman syndrome, can develop after uterine instrumentation (including curettage), pelvic infections, postobstetrical complications, and uterine surgery (posthysteroscopic myomectomy and polypectomy). In a large meta-analysis from 2014, relative to women with one miscarriage, women with two, three, or more miscarriages showed an increased intrauterine adhesion risk by a pooled odds ratio (OR) of 1.41 and 2.1, respectively (62). Case reports have described favorable pregnancy outcomes after adhesiolysis for mild to moderate adhesions; however, this was studied within an infertile population (63). Both the ESHRE and ASRM concluded that there was insufficient evidence to recommend surgical removal of IUAs in women with RPL (17, 18). Although there is a paucity of evidence supporting the surgical removal of intrauterine adhesions in couples with RPL, treatment of mild and moderate adhesions by a hysteroscopic approach may be considered. In the event of significant intrauterine adhesive disease or irreparable anatomic uterine abnormalities, IVF with transfer of embryos to an appropriately selected gestational carrier may also be a consideration.

## Summary statement

- *A uterine cavity evaluation should be offered to all women with unexplained RPL and can be considered in patients with aneuploid miscarriages to evaluate for anatomic abnormalities that could lead to miscarriage or sequelae from prior miscarriages, such as adhesions and retained pregnancy tissue. It is reasonable to offer surgical treatment of a uterine septum and acquired uterine defects, including endometrial polyps, submucosal fibroids,*

*retained pregnancy tissue, and intrauterine adhesions, in women with RPL.*

## PARENTAL KARYOTYPES

Although prior ASRM guidelines and ACOG recommend RPL couples undergo peripheral karyotyping to detect balanced structural chromosomal rearrangements, ESHRE and RCOG recommend parental karyotyping only after individual risk assessment or when testing of products of conception detects an unbalanced structural chromosomal abnormality (17–20). Routine karyotyping can miss small rearrangements or rearrangements that have similar banding patterns and are likely underestimated (64,65). A recent study involving over 1,000 RPL patients found that 11.7% of them had chromosomal abnormalities on low-pass sequencing, and 40% of these were undetected by G-banding karyotype (64, 66). Currently, only G-banding karyotype testing is widely available and should be considered the first test; however, further studies are needed on the optimal testing of parents desiring testing for chromosome rearrangements.

Testing for structural chromosomal rearrangements will provide reassurance for most couples, may help to individualize treatment plans, and respect reproductive autonomy. Furthermore, it aids genetic counseling for the affected individual(s) and their at-risk relatives. Accurate prediction of the risk of another miscarriage or birth of an affected child requires knowledge of the specific chromosomes involved, the type and size of the rearrangements, as well as the sex of the carrier (66). Additionally, prediction of the segregation mode in RPL patients presents further challenges because it is influenced by more factors, including the unique position of the translocation breakpoints in each patient, gene content, and other aspects unique to individual(s) (67). For individual(s) with reciprocal balanced translocations who elect assisted reproductive technologies (ART)/preimplantation genetic testing for structural rearrangements (PGT-SR), genetic counseling with risk calculation, counseling should include a discussion about 1) the increased risk of uniparental disomy (UPD) in their offspring (67–69), and 2) the possibly higher rates of additional aneuploid events among female carriers (67), although not all studies have shown this.

Arguments against routine parental karyotyping among those with RPL include the low chance of detecting an abnormality with <3 miscarriages, a negative family history, and maternal age above 39 years (18, 70–72), the reassuring cumulative LBRs without the adoption of invasive ART/PGT treatments (18), and the limitations and expenses associated with current karyotype technology. Furthermore, concerns exist about the unforeseen impact of the diagnosis on the parent(s)'s psychology and reproductive decision-making.

### Treatment options for carriers of balanced chromosomal rearrangements (PGT-SR)

Several observational studies on couples with translocations have shown LBRs as high as 70%–71% without assisted reproduction and miscarriage rates as low as 29%–30% (73,74). Treatment using IVF with PGT-SR can be offered to couples for whom one or both partners are carriers of a translocation. The PGT-SR can be utilized as a tool to screen embryos for an unbalanced chromosomal abnormality of parental origin. In addition, conception through the use of donor gametes can be considered in a couple where one or both partners carry a translocation.

To date, the efficiency of PGT-SR vs. expectant management has not been established, owing to the lack of prospective trials evaluating subsequent pregnancy outcomes and the relatively large number of different chromosome abnormalities that exist. Earlier studies on the use of preimplantation genetic diagnosis and cleavage-stage trophectoderm biopsy for translocation carriers had mixed outcomes regarding cumulative reduction in miscarriage rate and improvement in LBR (75, 76). A large, retrospective study of 194 couples with a reciprocal translocation and RPL who underwent 265 PGT-SR cycles described a LBR of 56% per euploid transfer and 38% per started cycle, with a miscarriage rate of 11.0% per clinical pregnancy (77). Patients should be counseled that the presence of a balanced translocation significantly decreases the number of euploid blastocysts available for transfer in an IVF cycle, and one study of 1942 PGT-SR cycles showed that on average, couples needed at least 4.5 blastocysts to have a good chance of at least one euploid embryo, which is consistent with another study showing 17%–22% euploidy rate depending on maternal age (78, 79). In the setting of advanced maternal age or low ovarian reserve, IVF is less likely to yield a euploid embryo and may require multiple retrieval cycles to achieve a usable embryo. These couples should be counseled on all options, including unassisted conception and donor gametes.

#### Summary statement

- *Screening for parental balanced structural chromosomal rearrangements should be offered when an unbalanced structural chromosome rearrangement is detected in miscarriage testing or when no chromosomal testing of miscarriages is available. Additional studies are warranted to determine the overall effectiveness of PGT-SR in the setting of parental chromosome rearrangements.*

## ANTIPHOSPHOLIPID SYNDROME TESTING

Antiphospholipid syndrome (APS) is an acquired thrombophilia, the diagnosis of which requires the presence of certain clinical criteria (i.e., thrombotic events and adverse pregnancy outcomes, including miscarriage) and the detection of persistent, circulating antiphospholipid antibodies (aPL) in the plasma on more than one occasion at least 12 weeks apart (80). The RPL patients with true APS are at risk for serious obstetrical complications, which can be life-threatening to both the mother and the fetus (19). The use of antithrombotic drugs during pregnancy may help prevent some of the adverse reproductive outcomes in this group; however, the data come from relatively small studies. The combination of aspirin and heparin appears to reduce the

risk of miscarriage associated with antiphospholipid antibody syndrome and therefore increase the rate of live births in a carefully defined cohort (81).

When and if to test patients with recurrent miscarriage is a matter of some controversy. Consensus guidelines state that testing is warranted if there are three or more consecutive miscarriages without other explanations; however, newer criteria suggest that recurrent early miscarriage alone may not be sufficient to meet clinical criteria for APS (82). Additionally, patients with a single miscarriage should be screened for other APS clinical criteria, such as documented miscarriage after 10 weeks, unexplained prior venous thromboembolism (VTE), and pregnancy complications, such as severe preterm preeclampsia, placental insufficiency, or cutaneous manifestations (see Table 3) (80, 83). Conversely, if all miscarriages are aneuploid, testing for aPL is not recommended. It should be recognized that APS testing has a high false positive rate, and repeat testing could cause delays in subsequent pregnancies or unnecessary treatments.

Laboratory testing should include lupus anticoagulant (LAC), anticardiolipin (aCL) immunoglobulin G (IgG) or immunoglobulin M (IgM), and anti-$\beta$2-glycoprotein-I (a$\beta$2GPI) immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies. Antibody titers >99th percentile for the laboratory or >40 IgG phospholipid units (GPL)/IgM phospholipid units (MPL) are considered preliminarily positive, but *need to be persistently positive* on repeat testing 12 weeks later to meet diagnostic criteria for APS (see Table 3) (80, 83, 84).

In 2023, the American Rheumatology Society and the European Alliance for the Associations of Rheumatology rigorously reviewed the literature and the available data to come up with a new scoring system that was statistically validated and approved for use in research settings (82). How these new research guidelines will be used in clinical practice is yet to be determined at the time that this document is being written.

### Treatment of APS

Although studies are small and inconsistent, a meta-analysis on the treatment of obstetric APS without a history of clot demonstrated the benefit of treatment with low-dose aspirin and prophylactic dose heparin/low molecular weight heparin (LMWH) (85). Current consensus guidelines recommend treating women with a history of thrombotic events and APS with therapeutic anticoagulation (86). Given the serious consequences of APS and the changing guidelines for testing and treatment, we recommend referral to a hematologist or rheumatologist with expertise in antiphospholipid antibody syndrome for long-term management of patients with confirmed persistent and moderate to high antibody titers and positive lupus anticoagulant.

### Summary statement

- *A laboratory evaluation for antiphospholipid antibodies is recommended for individuals who meet clinical criteria for antiphospholipid antibody syndrome. Treatment should include a low-dose aspirin before conception or with initiation of prophylactic heparin at the time of clinical or laboratory evidence of a pregnancy.*

## THYROID TESTING

Pregnancy impacts the function of the thyroid gland, and thyroid disease in pregnancy may lead to adverse obstetric and fetal outcomes. Among women trying to conceive, overt hypothyroidism is associated with an increased risk of infertility and miscarriage, with the risk of the latter calculated to be as high as 60% among hypothyroid women not treated adequately (87–90). For these reasons, the American Thyroid Association and ASRM recommend treating overt hypothyroidism with levothyroxine during pregnancy (91,92). There is some evidence of an association between 1) RPL and subclinical hypothyroidism and 2) RPL and thyroid autoimmunity (presence of elevated levels of thyroid peroxidase antibodies). A meta-analysis of five studies found the prevalence of subclinical hypothyroidism (SCH) in women with RPL to be 12.9% (95% CI: 0%–35%) (93), which is higher than the prevalence of SCH among pregnant women (3.5%). In a meta-analysis of 17 studies, Dong et al. (93) found an association between thyroid autoimmunity and RPL (OR 1.94; 95% CI, 1.43–2.64) (93). The ASRM recommends that women with RPL should be screened with a serum thyroid-stimulating hormone (TSH) (91).

### Treatment of thyroid dysfunction

Women with overt hypothyroidism, which is defined as TSH above the upper limit of normal for the laboratory, with free thyroxine (T4) below the normal range, should be adequately treated before planning the next pregnancy. There is also evidence that women with subclinical hypothyroidism, which is defined as TSH above the upper limit of normal for the laboratory, with free T4 in the normal range, and RPL should be treated with levothyroxine. In a 2023 meta-analysis of 15 studies, three studies of women with RPL and subclinical hypothyroidism found that levothyroxine treatment increased LBRs (RR = 1.20, 95% CI: 1.01, 1.42) and four studies found that levothyroxine treatment decreased miscarriage rates (RR = 0.65, 95%CI: 0.44, 0.97) compared with placebo (94). However, recent, large randomized controlled studies failed to show the benefit of treating euthyroid women with thyroid autoimmunity with levothyroxine (95–97).

### Summary statement

- *Women with RPL who have had euploid miscarriage or no testing of miscarriage tissue should be screened for hypothyroidism with measurement of TSH and treated if TSH >4 mIU/L or the upper limit of normal in the laboratory. Given the high-quality data demonstrating no benefit of treating euthyroid women with thyroid autoimmunity, we do not recommend screening for thyroid antibodies.*

## CHRONIC ENDOMETRITIS

Chronic endometritis is a subclinical inflammatory or infectious process characterized by the presence of plasma cells in the functional endometrium. There is a large body of evidence supporting the association between chronic endometritis and RPL, with a prevalence of 7%–57% (98–100), and

women with RPL have a significantly higher prevalence of chronic endometritis compared with controls (101, 102). A limitation of the current literature, however, is the use of varied testing methods, biopsy timing, and diagnostic criteria for defining chronic endometritis. Additionally, if other pathologies are present, such as polyps, retained products of conception, or fibroids, plasma cells may be seen in endometrial sampling and complicate the diagnosis.

Although hysteroscopy, endometrial culture, and microbiome testing have been proposed, the most well-studied method for the diagnosis of chronic endometritis is an endometrial biopsy with plasma cell identification. There is currently no consensus on the number of plasma cells required for the diagnosis and whether immunohistochemical staining for CD138 is necessary. One case control study evaluating various diagnostic thresholds suggests that the best performing criterion for chronic endometritis is identification of $\geq 3$ plasma cells per whole section or $\geq 2$ per 10 high-power field using CD138 staining (103).

### Treatment of chronic endometritis

Chronic endometritis is treated with oral antibiotics and removal of any associated uterine pathology (polyps, retained pregnancy tissue). A test of cure biopsy can be completed following the next menstrual cycle after antibiotic treatment. In 2010, Johnston-MacAnanny et al. (104) reported that a single course of doxycycline resulted in a cure among 66% of cases, while two courses of antibiotics resulted in a cure in all cases. In 2014, McQueen et al. (99) reported that treatment with levofloxacin and flagyl had a cure rate of 94% in a single course.

A meta-analysis of 12 studies examining the effects of antibiotic treatment of chronic endometritis in RPL patients showed improved LBR if a test of cure biopsy is performed and resolution of chronic endometritis confirmed. However, this data was limited by heterogeneous study populations, definitions of chronic endometritis, and a lack of RCTs (105, 106). A high-quality RCT presented as an abstract in which 438 women with RPL and biopsy confirmed chronic endometritis were randomized to 2 weeks of doxycycline vs. placebo demonstrated no significant difference in miscarriage or LBR (107, 108).

### Summary statement

- *Until recently, limited data existed to inform best practice and some evidence suggested a benefit to screening and treating endometritis. However, a recent high-quality RCT presented as an abstract demonstrated no benefit of prescribing doxycycline for chronic endometritis in RPL patients* (107, 108).

## MALE EVALUATION

Male age and metabolic health have been associated with miscarriage in several observational studies (109–111). However, standard semen analysis parameters do not appear to be predictive of RPL (112). In contrast, elevated sperm DNA fragmentation (SDF) is associated with miscarriage (113). Sperm DNA damage may occur from environmental toxins, pollution, drugs, febrile illness, cigarette smoking, varicocele, increasing paternal age, or a combination of factors (114–116). Sperm DNA is protected by protamines and tight packaging; however, despite these protections, certain regions of sperm DNA are still susceptible to damage (117). Some of this damage can be repaired by the oocyte after fertilization; however, in certain cases, the damage is too extensive for repair, and poor reproductive outcomes can occur.

Two recent meta-analyses have suggested that male partners of women with RPL have higher sperm DNA fragmentation than partners of fertile controls, with a mean difference of 11%–12% on the SDF scores (118, 119). In another meta-analysis, investigators found a higher rate of subsequent miscarriage in couples with high (vs. low) SDF, with RR = 2.16 (1.54, 3.03; $P \leq .00001$) (120).

### Treatment of male factors

Although interventions such as varicocele repair, testicular sperm extraction, sperm selection, smoking cessation, frequency of ejaculation, and other lifestyle optimization have been shown to decrease SDF, there are no well-controlled published studies that demonstrate whether treatment of elevated SDF decreases the risk of RPL. A large, randomized trial using hyaluronan binding for sperm selection did show a reduction in miscarriage rates, but this was not specifically focused on RPL patients (121). However, abnormal testing may prompt urologic consultation for men experiencing RPL, with the goal of identifying factors or interventions that could impact SDF (113, 122).

### Summary statement

- *Sperm DNA fragmentation testing may be considered in patients with otherwise unexplained recurrent miscarriage or recurrent miscarriage and concomitant infertility. Further research is necessary to determine if treatment improves pregnancy outcomes.*

## DIABETES MELLITUS TESTING

Uncontrolled diabetes mellitus (DM) and an elevated hemoglobin A1C (HbA1C) have both been linked to RPL; however, well-controlled DM is not a risk factor for RPL. In a recent study of patients with infertility and RPL, HbA1C was found to be superior to a 2-hr glucose tolerance test (GTT) as an initial screening test for pre-DM, because it identified a substantial number of women who would have remained undiagnosed on the basis of a normal 2-hr GTT alone (123). However, the clinical significance of an elevated HbA1C in women with infertility and RPL remains unclear.

**TABLE 3**

**Classification criteria for APS.**

| | |
|---|---|
| Clinical criteria | |
| Vascular thrombosis | • One or more documented episodes of arterial, venous, or small vessel thrombosis—other than superficial venous thrombosis—in any tissue or organ. Thrombosis must be confirmed by objective, validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall. |
| Pregnancy morbidity | • One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or direct examination of the fetus.<br>• One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency.<br>• Three or more unexplained, consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. |
| Laboratory criteria | |
| Note: Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criterion present (any combination); IIa, LAC present alone; and IIb, aCL present alone; IIc, anti-β2GPI antibody present alone. | • Lupus anticoagulant (LAC) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (84).<br>• Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 GPL or MPL, or > the 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.<br>• Anti-β2-glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile) present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures. |

*Note:* Adapted from Miyakis S et al. (80). AND Practice Bulletin No. (83). aCL = anticardiolipin antibody; APS = antiphospholipid syndrome; ELISA = enzyme-linked immunosorbent assay; GPL = IgG phospholipid; IgG = immunoglobulin G; IgM = immunoglobulin M; LAC = lupus anticoagulant; MPL = IgM phospholipid.

*American Society for Reproductive Medicine Practice Committee. Recurrent pregnancy loss. Fertil Steril 2026.*

## Summary statement

- *Given the association of uncontrolled DM with pregnancy complications and the need for glycemic control before conception to optimize outcomes, ASRM recommends measuring an HbA1C during the diagnostic workup of women with RPL if risk factors are present. Risk factors for DM include being overweight or obese (i.e., high body mass index [BMI]), family history of DM, age >40, polycystic ovary syndrome (PCOS), and history of gestational diabetes.*

## The use of metformin for women with PCOS

Polycystic ovary syndrome, obesity, and insulin resistance have been associated with increased risk of euploid miscarriage; however, the mechanisms are unclear (124, 125). The PCOS affects 5%–10% of the female population in the United States. Women with PCOS have difficulty conceiving and have been found to have an increased risk of miscarriage (126). Early miscarriage has been reported to be as high as 30%–50% in this population. Studies have implicated hyperinsulinemic insulin resistance as an independent risk factor for early miscarriage (127). Metformin, an insulin-sensitizing drug, has been shown to reduce the rate of early miscarriage in PCOS patients. Although not studied specifically in the setting of RPL, metformin has been shown to reduce miscarriage risk in women with PCOS in some observational studies (128–130). Metformin or placebo was administered to women with RPL and abnormal GTTs; miscarriage rates were significantly reduced after metformin therapy compared with placebo in women without PCOS (15% vs. 55%) (131). In a recent, large meta-analysis of 2,899 pregnant women with PCOS, the use of metformin significantly reduced the incidence of preterm delivery (3.86% vs 9.19%, RR 0.42, 95% CI 0.25–0.71, $P = .001$), early miscarriage (cumulative rate 6.58% vs 18.35%, RR 0.40, 95% CI 0.20–0.78, $P = .007$), and the use of insulin treatment throughout pregnancy (cumulative rate 2.14% vs 5.12%, RR 0.43, 95% CI 0.22–0.85, $P = .01$), all without any significant difference in serious maternal adverse events (132). However, continuous use of metformin throughout pregnancy, until delivery, has been associated with an increase in childhood obesity (133). A meta-analysis on the risks of metformin during pregnancy concluded that exposure to metformin during the first trimester of pregnancy does not increase the risk of birth defects (134). The currently available data are heterogeneous because of differences in patient populations and timing of initiation and discontinuation of metformin.

## Summary statement

- *Although the evidence of benefit in the setting of RPL is indirect, it is reasonable to consider metformin in women with PCOS, with evidence of insulin resistance and otherwise unexplained miscarriage. Further studies are needed*

*to clarify the optimal patient population, dosage, and timing of initiation and discontinuation before definitive recommendations can be made.*

## PROLACTIN TESTING

Prolactin is often measured in women with anovulatory infertility, because elevated levels are associated with ovulatory dysfunction and possible luteal phase defect. The latter might be mediating a negative impact of hyperprolactinemia on pregnancy outcomes. Earlier studies suggested a possible association between hyperprolactinemia and recurrent miscarriage (135, 136). However, there is no high-quality evidence either linking prolactin disturbances to RPL or documenting a benefit of dopamine agonist treatments on the prevention of future miscarriages in women with RPL.

### Summary statement

- *Prolactin testing is not recommended in women with RPL, except in the evaluation of coexisting clinical symptoms, such as galactorrhea or anovulation.*

## USE OF EMPIRIC PROGESTERONE

Progesterone is necessary to achieve and maintain pregnancy because of its direct effect on the endometrium and immune-modulating properties. There have been several studies evaluating the effect of progesterone supplementation on women with recurrent miscarriage, with differing conclusions. The Progesterone in Recurrent Miscarriage (PROMISE) trial was a large multicenter, randomized, placebo-controlled trial which showed that vaginal progesterone treatment in the first trimester of pregnancy did not result in a significant increase in LBR compared with placebo among patients with a history of unexplained recurrent miscarriage (137). This study was limited by the use of progesterone after a confirmed pregnancy. In 2017, Stephenson et al. (138), reported an improved LBR among women with RPL who used vaginal progesterone starting 3 days after the LH surge and until 10 weeks of gestation. However, this study was retrospective and nonrandomized.

The Progesterone in Spontaneous Miscarriage trial looked at the use of vaginal progesterone in patients who presented with vaginal bleeding in early pregnancy; there was a 3% increase in LBR, which was not significant. In a subgroup analysis of these studies, women with a history of miscarriage who present with threatened miscarriage had a 5% increase in LBR after the use of vaginal progesterone compared with placebo, which reached statistical significance. The investigators acknowledge that this observation requires further validation because multiple comparisons were performed without statistical adjustment (139). There is no evidence supporting the practice of checking progesterone levels in unassisted pregnancies and supplementing based on the level.

### Summary statement

- *Additional prospective clinical trials are needed to determine if progesterone supplementation in women with RPL can improve live birth rates. Vaginal progesterone may be considered in early pregnancy in the setting of vaginal bleeding and/or recurrent unexplained miscarriage using a shared decision-making model.*

## PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY

The most common cause of both sporadic and recurrent miscarriage is embryonic aneuploidy (140). Therefore, it has been hypothesized that IVF with preimplantation genetic testing for aneuploidy (PGT-A) could be an effective strategy to lower the rate of miscarriage and increase the LBR among individuals with recurrent miscarriage. However, PGT-A has not been shown to be effective at reducing miscarriage or increasing LBR in the setting of RPL in prospective studies (141).

In 2016, Murugappan et al. (142) performed a retrospective intent-to-treat analysis of IVF with PGT-A vs. expectant management (EM), where the decision to use PGT-A was based on provider recommendation and patient preference. In this study, an "attempt" was defined as one IVF cycle and frozen embryo transfer (FET) in the PGT-A group, as well as 6 months of trying to conceive in the EM group. The LBR in the two groups was similar, with 32% vs. 34% per attempt in PGT-A vs. EM. Furthermore, median time to pregnancy was longer in the cohort of women undergoing PGT-A vs. EM (6.5 vs. 3 months). In this analysis, improved LBR of PGT-A was only realized by patients >40 reaching euploid transfer (142).

In 2021, Bhatt et al. (143) performed a Society for Assisted Reproductive Technology – Clinic Outcome Reporting System (SART-CORS) analysis on IVF outcomes with or without PGT-A in individuals with RPL (N = 1,2631 cycles). The analysis was limited to couples with RPL, defined as a history of three or more miscarriages, undergoing FET with a primary outcome of live birth. In women with a diagnosis of RPL, the adjusted odds ratio (aOR) of live birth with FET with PGT-A vs. without PGT-A was 1.31 (95% CI: 1.12, 1.52) for age <35 years, 1.45 (95% CI: 1.21, 1.75) for ages 35–37 years, 1.89 (95% CI: 1.56, 2.29) for ages 38–40, 2.62 (95% CI: 1.94–3.53) for ages 41–42, and 3.80 (95% CI: 2.52, 5.72) for ages >42 years. The aOR for clinical miscarriage with PGT-A vs. without PGT-A was 0.95 (95% CI: 0.74, 1.21) for age <35 years, 0.85 (95% CI: 0.65, 1.11) for ages 35–37 years, 0.81 (95% CI: 0.60, 1.08) for ages 38–40, 0.86 (95% CI: 0.58, 1.27) for ages 41–42, and 0.58 (95% CI: 0.32, 1.07) for ages >42 years. This study has several limitations, including its retrospective study design and the control group being IVF patients without PGT-A, which therefore may be skewed toward worse prognosis patients with coexisting infertility (143). In a 2025 meta-analysis of retrospective and observational studies comparing IVF without PGT-A with IVF with PGT-A, there

was a statistical improvement in live birth per transfer with PGT-A, similar to that seen in the general IVF population (144). However, this analysis is similarly problematic to prior studies, as it did not analyze intent to treat per retrieval, cost, or time to pregnancy or include cycles with no embryos available for embryo transfer (ET), and, again, the control group (ET without PGT-A) is problematic in that IVF is not an established treatment for RPL. Although some observational studies demonstrate a reduction in miscarriage, miscarriage still occurs in 10%–20% of pregnancies after PGT-A (143, 144). Both studies, as well as the ASRM Practice Committee Opinion on the use of PGT-A, conclude that well-designed trials comparing outcomes of IVF with PGT-A to EM are needed before definitive recommendations can be made (143–145).

### Summary statement

- *Overall, PGT-A has not been shown to significantly reduce miscarriage or improve live births compared with EM in the setting of RPL. In women over 40 years with a proven aneuploid miscarriage, it is reasonable to discuss PGT-A using a shared decision-making model to reduce miscarriage because of aneuploidy. However, patients should be counseled that PGT-A has not been shown to reduce the time to successful pregnancy or increase LBR compared with EM. Prospective clinical trials in patients with RPL are needed.*

## THROMBOPHILIA WORKUP

In women with inherited thrombophilia, pregnancy can exaggerate the physiologically induced state of hypercoagulation and therefore increase the risk for thrombotic events. The possible role of inherited thrombophilias in RPL has generated a great deal of research interest, and an association between the two has been documented in a few meta-analyses. A recent systematic review of the prevalence of thrombophilia in women with RPL found it to be the same as that of the general population (146). Recommendations regarding testing are aimed at identifying women with RPL who might benefit from anticoagulation for the purposes of preventing recurrent VTE in pregnancy in accordance with current hematology guidelines.

### Use of empiric thrombolytics

The pathogenesis of unexplained RPL and recurrent miscarriage because of APS have potential similarities (147). On the basis of these similarities, thrombolytics such as LMWH and/or aspirin are often prescribed for patients with unexplained recurrent miscarriage. A randomized, placebo-controlled study (ALIFE) found that neither LMWH with aspirin vs. aspirin alone compared with placebo improved the LBR in patients with unexplained RPL (148). One study evaluated three different thrombolytic treatments (LMWH with aspirin, LMWH alone, aspirin alone) in women with RPL. Among patients who had a negative thrombophilia screen, all three treatments were equally effective when comparing LBR with miscarriage rate (149). A meta-analysis looked to compare the efficacy of heparin combined with aspirin vs. aspirin alone in patients with unexplained recurrent miscarriage. Four of the eight studies included in the meta-analysis included patients with thrombophilias. This study found that heparin with aspirin vs. aspirin alone increased the LBR in patients with unexplained RPL if the number of miscarriages was three or greater, but not after two miscarriages (150). A recent, international, multisite randomized controlled study examined the use of prophylactic use of LMWH in women with inherited thrombophilias and recurrent miscarriage (151). Outcomes were similar between treated and untreated women with LBRs of 72% (116/162) and 71% (112/158), respectively. A 2022 meta-analysis of seven randomized controlled studies including women with unexplained RPL did not show any benefit of LMWH or LMWH plus acetylsalicylic acid on miscarriage, live birth, or preeclampsia risk (152).

### Summary statement

- *Routine testing for thrombophilias is not recommended among women with RPL. The use of anticoagulants for the treatment of RPL with hereditary thrombophilias or unexplained RPL is not recommended, based on high-quality evidence showing no benefit on LBR or miscarriage rate.*

## OVARIAN RESERVE EVALUATION

Testing for ovarian reserve is not routinely recommended in the evaluation of women with RPL. However, some evidence exists suggesting a potential higher risk for miscarriage and RPL among younger women with diminished ovarian reserve (153–157). Studies are limited by small numbers, heterogeneity in the patient population, definition of diminished ovarian reserve, and tests utilized to determine the diagnosis, all of which limit the ability to pool the data and draw valid conclusions (153–157). Two large, prospective studies examining the association between antimüllerian hormone (AMH) and miscarriage have had conflicting results (158, 159). Further studies are needed to clarify the relationship between ovarian reserve testing, oocyte quality, ovarian function, and miscarriage before specific therapies can be proposed.

### Summary statement

- *The ASRM does not recommend routine testing for ovarian reserve in the evaluation of RPL because the association between RPL and ovarian reserve is unclear and no effective therapeutic interventions exist.*

## IMMUNE TESTING AND TREATMENT

The role of an altered immune environment as an etiology for unexplained RPL is supported by correlative studies and animal models demonstrating failed implantation and miscarriage in association with immune dysfunction. Clinical studies supporting a role for immune testing have been

significantly limited by study design, specifically low patient volume, lack of standardized immune testing, and poor reproducibility.

Clinical trials evaluating immune therapies have similarly suffered from poor study design (i.e., limited RCTs) and nonspecific immunomodulating therapies without clear endpoints for treatment. Given the great interest in immune investigations and treatment by patients and reproductive immunologists, we must continue to investigate immune testing and treatment in subgroups of RPL patients most likely to benefit (i.e., those with recurrent euploid miscarriages) under research protocols before recommendations can be made.

### Summary statement

- *The ASRM does not recommend routine immune testing and treatment in the evaluation of RPL.*

## PREPREGNANCY EVALUATION AND CARE

Optimization of all maternal health, autoimmune conditions, and medications before pregnancy should be attempted for all women as part of a comprehensive preconception counseling (160).

All women planning pregnancy, regardless of fertility or miscarriage history, should be counseled for healthy lifestyle changes, prenatal folic acid support, and avoidance of toxic exposures during the periconception period. Tobacco usage and secondhand smoke are linked to an increased risk of sporadic miscarriage (161, 162). Cessation of tobacco and limiting exposure to secondhand smoke are recommended (19, 163). The role of alcohol and caffeine is less clear, and studies are mixed. However, there may be an interaction or dose response to these common exposures. Alcohol consumption (>3 drinks per week) and caffeine consumption (>99 mg/day) have been associated with an increased risk of miscarriage or recurrent miscarriage (164–166). The effect of stopping caffeine use has not been evaluated in any trial. Low or moderate exercise is not associated with miscarriage. The data on high-intensity exercise and occupational activities is less clear and has been associated with miscarriage in some studies (167). Obesity has also been found to be an independent risk factor for miscarriage in patients with recurrent miscarriage, and it has also been associated with euploid miscarriage in IVF-FET cycles (168, 169); however, no study has evaluated the impact of weight loss on miscarriage rate in this population.

### Summary statement

- *Although the data on lifestyle interventions on miscarriage risk are limited, given the known risk of certain exposures in pregnancy and the possible impact on miscarriage risk, these exposures should be reduced whenever possible preconception. Smoking cessation is strongly recommended.*

## PSYCHOLOGICAL FACTORS AND SUPPORT

It has long been recognized that women experiencing RPL are subject to significant psychological sequelae, including an increased risk of depression, anxiety, posttraumatic stress, guilt, and anger, with the incidence of depression approximately five times higher in women affected by RPL (170–172). Although most of the psychological data within RPL focuses on the female partner's experience, there has been evolving research into the impact of RPL on the male partner. In a cross-sectional study in couples experiencing RPL, the investigators demonstrate that while women are more likely to experience depression and anxiety, male partners of women with RPL are also at significant risk for these symptoms, and both men and women reported limited social support (172). It is clear that miscarriage exacts an immense psychological toll on the affected couple as a dyad. Unfortunately, there is little data on the miscarriage experience of underrepresented groups, such as racial, ethnic, and sexual minorities; research is needed to address these gaps in knowledge. Healthcare professionals should validate the individual's experience, implement screening for mood disorders and social support for women and their partners, and offer referral to mental health professionals for counseling support to all patients experiencing miscarriage, while simultaneously not assigning blame to patients and reminding patients that the most common cause of miscarriage is a genetically abnormal embryo.

Several studies, including a meta-analysis published in 2017, demonstrated a positive correlation between maternal stress and miscarriage (173). Two nonrandomized studies have examined the impact of supportive care in subsequent pregnancy (11, 174). A cohort of 158 couples with three or more otherwise unexplained consecutive miscarriages was divided into two groups, with one receiving routine obstetrical care during the next pregnancy (n = 42) and the other additionally receiving tender-loving care (TLC) (n = 116). The TLC was defined as psychological support with weekly medical and ultrasonographic examinations, as well as instructions to avoid heavy work, travel, and sexual activity. The difference in live births was significant: 36% in the control group and 85% in the TLC group.

### Summary statement

- *The RPL couples are at risk for psychological sequelae. Psychological support is an essential part of miscarriage care and should be offered to all couples experiencing miscarriage and planning future pregnancy.*

## SUMMARY

The following statements address specific aspects of testing and treating couples or individuals with RPL:

- ASRM defines recurrent pregnancy loss (RPL) as the spontaneous loss of two or more pregnancies, excluding confirmed molar or ectopic pregnancies. Pregnancies confirmed by urinary or blood HCG are sufficient.
- ASRM recommends chromosome analysis of miscarriage tissue, when feasible, as a first step in the evaluation of

the couple with RPL. ASRM joins ESHRE and ACOG in recommending array-based technology for analysis of miscarriage tissue on the basis of its many technical advantages over traditional cytogenetic analysis. Options for at-home collection of tissue for miscarriage tissue testing should be discussed with patients at the time of miscarriage for patients who do not desire surgical management.

- A uterine cavity evaluation should be offered to all women with unexplained RPL and can be considered in patients with aneuploid miscarriages to evaluate for anatomic abnormalities that could lead to miscarriage or sequelae from prior miscarriages, such as adhesions and retained pregnancy tissue. It is reasonable to offer surgical treatment of a uterine septum and acquired uterine defects, including endometrial polyps, submucosal fibroids, retained pregnancy tissue, and intrauterine adhesions, in women with RPL.
- Screening for parental balanced structural chromosomal rearrangements should be offered when an unbalanced structural chromosome rearrangement is detected in miscarriage testing or when no chromosomal testing of miscarriages is available. Additional studies are warranted to determine the overall effectiveness of PGT-SR in the setting of parental chromosome rearrangements.
- A laboratory evaluation for antiphospholipid antibodies is recommended for individuals who meet clinical criteria for antiphospholipid antibody syndrome. Treatment should include a low-dose aspirin before conception or with initiation of prophylactic heparin at the time of clinical or laboratory evidence of a pregnancy.
- Women with RPL who have had euploid miscarriage or no testing of miscarriage tissue should be screened for hypothyroidism with measurement of TSH and treated if TSH >4 mIU/L or the upper limit of normal in the laboratory. Given the high-quality data demonstrating no benefit of treating euthyroid women with thyroid autoimmunity, we do not recommend screening for thyroid antibodies.
- Until recently, limited data existed to inform best practice, and some evidence suggested a benefit to screening and treating endometritis. However, a recent high-quality RCT presented as an abstract demonstrated no benefit of prescribing doxycycline for chronic endometritis in RPL patients.
- Sperm DNA fragmentation testing may be considered in patients with otherwise unexplained recurrent miscarriage or RPL and concomitant infertility. Further research is necessary to determine if treatment improves pregnancy outcomes.
- Given the association of uncontrolled DM with pregnancy complications and the need for glycemic control before conception to optimize outcomes, ASRM recommends measuring an HbA1C during the diagnostic workup of women with RPL if risk factors are present. Risk factors for DM include being overweight or obese (i.e., high BMI), family history of DM, age >40, PCOS, and history of gestational diabetes.
- Although the evidence of benefit in the setting of RPL is indirect, it is reasonable to consider metformin in women with PCOS, with evidence of insulin resistance and otherwise unexplained miscarriage. Further studies are needed to clarify the optimal patient population, dosage, and timing of initiation and discontinuation before definitive recommendations can be made.
- Prolactin testing is not recommended in women with RPL, except in the evaluation of coexisting clinical symptoms, such as galactorrhea or anovulation.
- Additional prospective clinical trials are needed to determine if progesterone supplementation in women with RPL can improve live birth rates. Vaginal progesterone may be offered in early pregnancy in the setting of vaginal bleeding and/or recurrent unexplained miscarriage using a shared decision-making model.
- Overall, PGT-A has not been shown to significantly reduce miscarriage or improve live births compared with EM in the setting of RPL. In women over 40 years with a proven aneuploid miscarriage, it is reasonable to discuss PGT-A using a shared decision-making model to reduce miscarriage because of aneuploidy. However, patients should be counseled that PGT-A has not been shown to reduce the time to successful pregnancy or increase live birth rate compared with EM. Prospective clinical trials in patients with RPL are needed.
- Routine testing for thrombophilias is not recommended among women with RPL. The use of anticoagulants for the treatment of RPL with hereditary thrombophilias or unexplained RPL is not recommended, on the basis of high-quality evidence showing no benefit on livebirth or miscarriage rate.
- ASRM does not recommend routine testing for ovarian reserve in the evaluation of RPL because the association between RPL and ovarian reserve is unclear and no effective therapeutic interventions exist.
- ASRM does not recommend routine immune testing and treatment in the evaluation of RPL.
- Although the data on lifestyle interventions on miscarriage risk are limited, given the known risk of certain exposures in pregnancy and the possible impact on miscarriage risk, these exposures should be reduced whenever possible preconception. Smoking cessation is strongly recommended.
- The RPL couples are at risk for psychological sequelae. Psychological support is an essential part of miscarriage care and should be offered to all couples experiencing miscarriage and planning future pregnancy.

## CONCLUSIONS

RPL is identified in a woman with the loss of two or more presumed intrauterine pregnancies before 22 completed weeks of pregnancy. An algorithm is presented that guides the diagnostic workup on the basis of the chromosome status of the second miscarriage, while still allowing for provider judgment for higher numbers of miscarriages or untested miscarriages.

In this updated Committee Opinion, etiologies and treatments for RPL are presented in the context of the latest research advances in the field. One of the biggest challenges of treating patients with unexplained recurrent miscarriage is the high percentage of patients who remain unexplained if chromosome testing of the miscarriage is not performed, which can compel patients to request unproven diagnostic tests and therapies. Although ASRM supports shared decision-making, counseling patients with this multifactorial disorder should include an evidence-based approach in a supportive environment to minimize risks of unproven treatments. Expectant management should be discussed as a viable option, as the success rate is 50%–80% for the majority of patients with unexplained RPL (11, 174). As researchers and providers, it is essential that we continue to work to find patients' answers and effective treatments and to continue to critically evaluate the literature as it emerges. Further research is needed in several areas, such as genetic and immune predisposition to miscarriage, endometrial factors, and therapies to mitigate the psychological impact of miscarriage on families. Empiric use of other treatment modalities has been suggested for unexplained RPL. However, studies have not shown benefit to RPL patients with routine use of low-dose aspirin, enoxaparin, glucocorticoids, heparin, endometrial scratching, granulocyte-colony stimulating factor (G-CSF), intralipid therapy, routine use vaginal progesterone, alloimmune causes, or treatment with intravenous immunoglobulin (IVIG), or lymphocyte immunization therapy. At the present time, the use of empiric thrombolytics is not recommended for unexplained RPL.

## Acknowledgments

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## REFERENCES

1. Kolte AM, Van Oppenraaij RH, Quenby S, Farquharson RG, Stephenson M, Goddijn M, et al. Non-visualized pregnancy losses are prognostically important for unexplained recurrent miscarriage. Hum Reprod 2014;29:931–7.
2. Rodgers SK, Horrow MM, Doubilet PM, Frates MC, Kennedy A, Andreotti R, et al. A lexicon for first-trimester US: Society of Radiologists in Ultrasound Consensus Conference recommendations. Radiology 2024;312:e240122.
3. Rodgers SK, Horrow MM, Doubilet PM, Frates MC, Kennedy A, Andreotti R, et al. A Lexicon for first-trimester US: Society of Radiologists in Ultrasound Consensus Conference recommendations. Am J Obstet Gynecol 2025;232:1–16.
4. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, De Mouzon J, Sokol R, et al. The international glossary on infertility and fertility care, 2017. Fertil Steril 2017;108:393–406.
5. Management of stillbirth: obstetric care consensus no, 10. Obstet Gynecol 2020;135:e110–32.
6. World Health Organization. Improving maternal and newborn health and survival and reducing stillbirth - Progress report 2023. Available at: https://www.who.int/publications/i/item/9789240073678. Accessed March 3, 2026.
7. Hassold T, Chen N, Funkhouser J, Jooss T, Manuel B, Matsuura J, et al. A cytogenetic study of 1000 spontaneous abortions. Ann Hum Genet 1980;44:151–78.
8. Milunsky A, Milunsky JM, editors. Genetic disorders and the fetus: diagnosis, prevention and treatment. 6th ed. Baltimore, MD: Wiley; 2010:194–200.
9. Westergaard D, Nielsen AP, Mortensen LH, Nielsen HS, Brunak S. Phenome-wide analysis of short- and long-run disease incidence following recurrent pregnancy loss using data from a 39-year period. J Am Heart Assoc 2020;9:e015069.
10. Egerup P, Kolte AM, Larsen EC, Krog M, Nielsen HS, Christiansen OB. Recurrent pregnancy loss: what is the impact of consecutive versus non-consecutive losses? Hum Reprod 2016;31:2428–34.
11. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999;14:2868–71.
12. Sugiura-Ogasawara M, Ozaki Y, Katano K, Suzumori N, Kitaori T, Mizutani E. Abnormal embryonic karyotype is the most frequent cause of recurrent miscarriage. Hum Reprod 2012;27:2297–303.
13. Bernardi LA, Plunkett BA, Stephenson MD. Is chromosome testing of the second miscarriage cost saving? A decision analysis of selective versus universal recurrent pregnancy loss evaluation. Fertil Steril 2012;98:156–61.
14. Brezina PR, Kutteh WH. Classic and cutting-edge strategies for the management of early pregnancy loss. Obstet Gynecol Clin North Am 2014;41:1–18.
15. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Hum Reprod 2018;33:579–87.
16. Murugappan G, Leonard SA, Newman H, Shahine L, Lathi RB. Karyotype of first clinical miscarriage and prognosis of subsequent pregnancy outcome. Reprod Biomed Online 2021;42:1196–202.

17. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103–11.
18. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2018; 2018:hoy004.
19. Royal College of Obstetricians and Gynaecologists. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. London, UK: RCOG; 2011.
20. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 200: early pregnancy loss. Obstet Gynecol 2018;132:e197–207.
21. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod 2002;17:446–51.
22. Kutteh WH, Papas RS, Maisenbacher MK, Dahdouh EM. Role of genetic analysis of products of conception and PGT in managing early pregnancy loss. Reprod Biomed Online 2024;49:103738.
23. Mcnally L, Huynh D, Keller J, Dikan J, Rabinowitz M, Lathi RB. Patient experience with karyotyping after first trimester miscarriage: a national survey. J Reprod Med 2016;61:128–32.
24. Foyouzi N, Cedars MI, Huddleston HG. Cost-effectiveness of cytogenetic evaluation of products of conception in the patient with a second pregnancy loss. Fertil Steril 2012;98:151–5.
25. Siegel M, Amato P, Lee D, Wu D, Krieg S. Home collection of products of conception: can chromosomal analysis be obtained? J Gynecol Obstet Hum Reprod 2021;50:101810.
26. Kaser DMD. The status of genetic screening in recurrent pregnancy loss. Obstet Gynecol Clin North Am 2018;45:143–54.
27. Lomax B, Tang S, Separovic E, Phillips D, Hillard E, Thomson T, et al. Comparative genomic hybridization in combination with flow cytometry improves results of cytogenetic analysis of spontaneous abortions. Am J Hum Genet 2000;66:1516–21.
28. Robberecht C, Schuddinck V, Fryns J-P, Vermeesch JR. Diagnosis of miscarriages by molecular karyotyping: benefits and pitfalls. Genet Med 2009; 11:646–54.
29. Sahoo T, Dzidic N, Strecker MN, Commander S, Travis MK, Doherty C, et al. Comprehensive genetic analysis of pregnancy loss by chromosomal microarrays: outcomes, benefits, and challenges. Genet Med 2017;19:83–9.
30. Shah MS, Cinnioglu C, Maisenbacher M, Comstock I, Kort J, Lathi RB. Comparison of cytogenetics and molecular karyotyping for chromosome testing of miscarriage specimens. Fertil Steril 2017;107:1028–33.
31. Van Den Berg MM, Van Maarle MC, Van Wely M, Goddijn M. Genetics of early miscarriage. Biochim Biophys Acta 2012;1822:1951–9.
32. Shearer BM, Thorland EC, Carlson AW, Jalal SM, Ketterling RP. Reflex fluorescent in situ hybridization testing for unsuccessful product of conception cultures: a retrospective analysis of 5555 samples attempted by conventional cytogenetics and fluorescent in situ hybridization. Genet Med 2011;13:545–52.
33. Kudesia R, Li M, Smith J, Patel A, Williams Z. Rescue karyotyping: a case series of array-based comparative genomic hybridization evaluation of archival conceptual tissue. Reprod Biol Endocrinol 2014;12:19, 9.
34. Mathur N, Triplett L, Stephenson MD. Miscarriage chromosome testing: utility of comparative genomic hybridization with reflex microsatellite analysis in preserved miscarriage tissue. Fertil Steril 2014;101: 1349–52.
35. Lathi RB, Gustin SL, Keller J, Maisenbacher MK, Sigurjonsson S, Tao R, et al. Reliability of 46,XX results on miscarriage specimens: a review of 1,222 first-trimester miscarriage specimens. Fertil Steril 2014;101:178–82.
36. Murugappan G, Gustin S, Lathi RB. Separation of miscarriage tissue from maternal decidua for chromosome analysis. Fertil Steril 2014;102:e9–10.
37. Tamura Y, Santo M, Araki Y, Matsubayashi H, Takaya Y, Kitaya K, et al. Chromosomal copy number analysis of products of conception by conventional karyotyping and next-generation sequencing. Reprod Med Biol 2021;20:71–5.
38. Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. Hum Reprod Update 2011;17:761–71.
39. Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. Hum Reprod Update 2008;14:415–29.
40. Venetis CA, Papadopoulos SP, Campo R, Gordts S, Tarlatzis BC, Grimbizis GF. Clinical implications of congenital uterine anomalies: a meta-analysis of comparative studies. Reprod Biomed Online 2014;29: 665–83.
41. Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, Van Schoubroeck D, et al. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Gynecol Surg 2016;13:1–16.
42. Pfeifer SM, Attaran M, Goldstein J, Lindheim SR, Petrozza JC, Rackow BW, et al. ASRM müllerian anomalies classification 2021. Fertil Steril 2021;116: 1238–52.
43. Ludwin A, Ludwin I, Banas T, Knafel A, Miedzyblocki M, Basta A. Diagnostic accuracy of sonohysterography, hysterosalpingography and diagnostic hysteroscopy in diagnosis of arcuate, septate and bicornuate uterus. J Obstet Gynaecol Res 2011;37:178–86.
44. Muñoz E, Fernández I, Pellicer N, Mariani G, Pellicer A, Garrido N. Reproductive outcomes of oocyte donation in patients with uterine müllerian anomalies. Fertil Steril 2023;120:850–9.
45. Gundabattula SR, Joseph E, Marakani LR, Dasari S, Nirmalan PK. Reproductive outcomes after resection of intrauterine septum. J Obstet Gynaecol 2014;34:235–7.
46. Pang LH, Li MJ, Li M, Xu H, Wei ZL. Not every subseptate uterus requires surgical correction to reduce poor reproductive outcome. Int J Gynaecol Obstet 2011;115:260–3.
47. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215–23.
48. Sugiura-Ogasawara M, Lin BL, Aoki K, Maruyama T, Nakatsuka M, Ozawa N, et al. Does surgery improve live birth rates in patients with recurrent miscarriage caused by uterine anomalies? J Obstet Gynaecol 2015; 35:155–8.
49. Carrera M, Pérez Millan F, Alcázar JL, Alonso L, Caballero M, Carugno J, et al. Effect of hysteroscopic metroplasty on reproductive outcomes in women with septate uterus: systematic review and meta-analysis. J Minim Invasive Gynecol 2022;29:465–75.
50. Rikken JFW, Verhorstert KWJ, Emanuel MH, Bongers MY, Spinder T, Kuchenbecker WKH, et al. Septum resection in women with a septate uterus: a cohort study. Hum Reprod 2020;35:1578–88.
51. Whelan A, Burks C, Stephenson MD. Pregnancy outcomes in women with a history of recurrent early pregnancy loss and a septate uterus, with and without hysteroscopic metroplasty. Obstet Gynecol 2020; 136:417–9.
52. Rikken JFW, Kowalik CR, Emanuel MH, Bongers MY, Spinder T, Jansen FW, et al. Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. Hum Reprod 2021;36:1260–7.
53. Practice Committee of the American Society for Reproductive Medicine. Evidence-based diagnosis and treatment for uterine septum: a guideline. Fertil Steril 2024;122:251–65.
54. Carbonnel M, Pirtea P, De Ziegler D, Ayoubi JM. Uterine factors in recurrent pregnancy losses. Fertil Steril 2021;115:538–45.
55. Saravelos SH, Yan J, Rehmani H, Li TC. The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage. Hum Reprod 2011;26:3274–9.
56. Olive DL, Pritts EA. Fibroids and reproduction. Semin Reprod Med 2010; 28:218–27.
57. Jansen FW, Vredevoogd CB, Van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. Obstet Gynecol 2000;96:266–70.
58. Lieng M, Istre O, Qvigstad E. Treatment of endometrial polyps: a systematic review. Acta Obstet Gynecol Scand 2010;89:992–1002.
59. Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, et al. Endometrial polyps and their implication in the pregnancy

rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod 2005;20:1632–5.
60. Kuroda K, Yamanaka A, Takamizawa S, Nakao K, Kuribayashi Y, Nakagawa K, et al. Prevalence of and risk factors for chronic endometritis in patients with intrauterine disorders after hysteroscopic surgery. Fertil Steril 2022;118:568–75.
61. Volodarsky-Perel A, Badeghiesh A, Shrem G, Steiner N, Tulandi T. Chronic endometritis in fertile and infertile women who underwent hysteroscopic polypectomy. J Minim Invasive Gynecol 2020;27:1112–8.
62. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brölmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update 2014;20:262–78.
63. Choudhary P, Singh V. Hysteroscopic intrauterine adhesiolysis resulting in positive reproductive outcome. Gynecol Minim Invasive Ther 2019;8:192–3.
64. Dong Z, Wang H, Chen H, Jiang H, Yuan J, Yang Z, et al. Identification of balanced chromosomal rearrangements previously unknown among participants in the 1000 Genomes Project: implications for interpretation of structural variation in genomes and the future of clinical cytogenetics. Genet Med 2018;20:697–707.
65. Redin C, Brand H, Collins RL, Mitchell E, Pillalamarri V, Seabra CM, et al. The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies. Nat Genet 2017;49:36–45.
66. Dong Z, Yan J, Xu F, Yuan J, Jiang H, Wang H, et al. Genome sequencing explores complexity of chromosomal abnormalities in recurrent miscarriage. Am J Hum Genet 2019;105:1102–11.
67. Verdoni A, Hu J, Surti U, Babcock M, Sheehan E, Clemens M, et al. Reproductive outcomes in individuals with chromosomal reciprocal translocations. Genet Med 2021;23:1753–60.
68. Behnecke A, Hinderhofer K, Jauch A, Janssen JWG, Moog U. Silver-Russell syndrome due to maternal uniparental disomy 7 and a familial reciprocal translocation t(7;13). Clin Genet 012;82:494–498.
69. Liehr T. Cytogenetic contribution to uniparental disomy (UPD). Mol Cytogenet 2010;3:8.
70. Barber JCK, Cockwell AE, Grant E, Williams S, Dunn R, Ogilvie CM. Is karyotyping couples experiencing recurrent miscarriage worth the cost? Br J Obstet Gynaecol 2010;117:885–8.
71. Franssen MTM, Korevaar JC, Leschot NJ, Bossuyt PMM, Knegt AC, Gerssen-Schoorl KBJ, et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. Br Med J 2005;331:137–9.
72. Franssen MTM, Korevaar JC, Van Der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: index [corrected]-control study. Br Med J 2006;332:759–63.
73. Goddijn M, Joosten JHK, Knegt AC, Van Derveen F, Franssen MTM, Bonsel GJ, et al. Clinical relevance of diagnosing structural chromosome abnormalities in couples with repeated miscarriage. Hum Reprod 2004;19:1013–7.
74. Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod 2006;21:1076–82.
75. Pundir J, Magdalani L, El-Toukhy T. Outcome of preimplantation genetic diagnosis using FISH analysis for recurrent miscarriage in low-risk reciprocal translocation carriers. Eur J Obstet Gynecol Reprod Biol 2016;203:214–9.
76. Sugiura-Ogasawara M, Ozaki Y, Sato T, Suzumori N, Suzumori K. Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translocations. Fertil Steril 2004;81:367–73.
77. Huang C, Jiang W, Zhu Y, Li H, Lu J, Yan J, et al. Pregnancy outcomes of reciprocal translocation carriers with two or more unfavorable pregnancy histories: before and after preimplantation genetic testing. J Assist Reprod Genet 2019;36:2325–31.
78. Liu M, Bu Z, Liu Y, Liu J, Dai S. Are ovarian responses and the number of transferable embryos different in females and partners of male balanced translocation carriers? J Assist Reprod Genet 2022;39:2019–26.
79. Yamazaki A, Kuroda T, Kawasaki N, Kato K, Shimojima Yamamoto K, Iwasa T, et al. Preimplantation genetic testing using comprehensive genomic copy number analysis is beneficial for balanced translocation carriers. J Hum Genet 2024;69:41–5.
80. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
81. Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database Syst Rev 2020;5:Cd012852.
82. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo M-C, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687–702.
83. Practice Bulletin No. 132: antiphospholipid syndrome. Obstetrics and gynecology 2012;120:151421.
84. Devreese KMJ, Bertolaccini ML, Branch DW, De Laat B, Erkan D, Favaloro EJ, et al. An update on laboratory detection and interpretation of antiphospholipid antibodies for diagnosis of antiphospholipid syndrome: guidance from the ISTH-SSC Subcommittee on lupus anticoagulant/antiphospholipid antibodies. J Thromb Haemost 2025;23:731–44.
85. Hamulyák EN, Scheres LJJ, Goddijn M, Middeldorp S. Antithrombotic therapy to prevent recurrent pregnancy loss in antiphospholipid syndrome-what is the evidence? J Thromb Haemost 2021;19:1174–85.
86. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e691S–736S.
87. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63–8.
88. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549–55.
89. Van Den Boogaard E, Vissenberg R, Land JA, Van Wely M, Van Der Post JaM, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod update 2011;17:605–19.
90. Vissenberg R, Van Dijk MM, Fliers E, Van Der Post JaM, Van Wely M, Bloemenkamp KWM, et al. Effect of levothyroxine on live birth rate in euthyroid women with recurrent miscarriage and TPO antibodies (T4-LIFE study). Contemp Clin Trials 2015;44:134–8.
91. Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril 2015;104:545–53.
92. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315–89.
93. Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2020;113:587600.e1.
94. Yu M, Long Y, Wang Y, Zhang R, Tao L. Effect of levothyroxine on the pregnancy outcomes in recurrent pregnancy loss women with subclinical hypothyroidism and thyroperoxidase antibody positivity: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2023;36:2233039.
95. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med 2019;380:131625.
96. Van Dijk MM, Vissenberg R, Fliers E, Van Der Post JaM, Van Der Hoorn MP, De Weerd S, et al. Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2022;10:322–9.

97. Wang H, Gao H, Chi H, Zeng L, Xiao W, Wang Y, et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: a randomized clinical trial. J Am Med Assoc 2017;318:2190–8.
98. Cicinelli E, Matteo M, Tinelli R, Pinto V, Marinaccio M, Indraccolo U, et al. Chronic endometritis due to common bacteria is prevalent in women with recurrent miscarriage as confirmed by improved pregnancy outcome after antibiotic treatment. Reprod Sci 2014;21:640–7.
99. Mcqueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. Fertil Steril 2014;101:1026–30.
100. McQueen DB, Perfetto CO, Hazard FK, Lathi RB. Pregnancy outcomes in women with chronic endometritis and recurrent pregnancy loss. Fertil Steril 2015;104:927–31.
101. Mcqueen DB, Maniar KP, Hutchinson A, Confino R, Bernardi L, Pavone ME. Redefining chronic endometritis: the importance of endometrial stromal changes. Fertil Steril 2021;116:855–61.
102. Zolghadri J, Momtahan M, Aminian K, Ghaffarpasand F, Tavana Z. The value of hysteroscopy in diagnosis of chronic endometritis in patients with unexplained recurrent spontaneous abortion. Eur J Obstet Gynecol Reprod Biol 2011;155:217–20.
103. Liu Y, Chen X, Huang J, Wang CC, Yu MY, Laird S, et al. Comparison of the prevalence of chronic endometritis as determined by means of different diagnostic methods in women with and without reproductive failure. Fertil Steril 2018;109:832–9.
104. Johnston-Macananny EB, Hartnett J, Engmann LL, Nulsen JC, Sanders MM, Benadiva CA. Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. Fertil Steril 2010;93:437–41.
105. Kimura F, Takebayashi A, Ishida M, Nakamura A, Kitazawa J, Morimune A, et al. Review: chronic endometritis and its effect on reproduction. J Obstet Gynaecol Res 2019;45:951–60.
106. Pirtea P, Cicinelli E, De Nola R, De Ziegler D, Ayoubi JM. Endometrial causes of recurrent pregnancy losses: endometriosis, adenomyosis, and chronic endometritis. Fertil Steril 2021;115:546–60.
107. Odendaal J, Black N, Bouliotis G, Guck J, Underwood M, Fisher J, et al. Preconceptual administration of doxycycline in women with recurrent miscarriage and chronic endometritis: protocol for the Chronic Endometritis and Recurrent Miscarriage (CERM) trial, a multicentre, double-blind, placebo-controlled, adaptive randomised trial with an embedded translational substudy. Br Med J Open 2023;13:e081470.
108. Quenby S, Odendaal J, Black N, Fishwick K, Thornton J, Makwana K, et al. O-023 Double blind randomised controlled trial of doxycycline in women with recurrent miscarriage and chronic endometritis: the CERM trial. Hum Reprod 2025;40:deaf097.023.
109. Du Fossé NA, Van Der Hoorn MP, Van Lith JMM, Le Cessie S, Lashley E. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Hum Reprod Update 2020;26:650–69.
110. Kasman AM, Zhang CA, Li S, Lu Y, Lathi RB, Stevenson DK, et al. Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data. Hum Reprod 2021;36:785–93.
111. Marsidi AM, Kipling LM, Kawwass JF, Mehta A. Influence of paternal age on assisted reproductive technology cycles and perinatal outcomes. Fertil Steril 2021;116:380–7.
112. Hill JA, Abbott AF, Politch JA. Sperm morphology and recurrent abortion. Fertil Steril 1994;61:776–8.
113. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril 2021;115:54–61.
114. Rubes J, Selevan SG, Evenson DP, Zudova D, Vozdova M, Zudova Z, et al. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum Reprod 2005;20:2776–83.
115. Shamsi MB, Venkatesh S, Kumar R, Gupta NP, Malhotra N, Singh N, et al. Antioxidant levels in blood and seminal plasma and their impact on sperm parameters in infertile men. Indian J Biochem Biophys 2010;47:38–43.
116. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol 2013;11:66, 6.
117. Agarwal A, Majzoub A, Esteves SC, Ko E, Ramasamy R, Zini A. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. Transl Androl Urol 2016;5:935–50.
118. Mcqueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2019;112:54–60.e3.
119. Tan J, Taskin O, Albert A, Bedaiwy MA. Association between sperm DNA fragmentation and idiopathic recurrent pregnancy loss: a systematic review and meta-analysis. Reprod Biomed Online 2019;38:951–60.
120. Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod 2012;27:2908–17.
121. West R, Coomarasamy A, Frew L, Hutton R, Kirkman-Brown J, Lawlor M, et al. Sperm selection with hyaluronic acid improved live birth outcomes among older couples and was connected to sperm DNA quality, potentially affecting all treatment outcomes. Hum Reprod 2022;37:1106–25.
122. Rios JS, Coward RM, Hansen KR, Barnhart KT, Cedars MI, Legro RS, et al. Sperm deoxyribonucleic acid fragmentation: predictors, fertility outcomes, and assays among infertile males. F S Rep 2021;2:282–8.
123. Shapiro AJ, Holden EC, Mcgovern PG, Alderson D, Morelli SS. Comparison of 2-hour oral glucose tolerance test and hemoglobin A1C in the identification of pre-diabetes in women with infertility and recurrent pregnancy loss. Clin Med Insights Reprod Health 2019;13:1179558119831280.
124. Boots CE, Stephenson MD. Does obesity increase the rate of miscarriage in spontanous conception: a systematic review. Fertil Steril 2011;96:S284.
125. Landres IV, Milki AA, Lathi RB. Karyotype of miscarriages in relation to maternal weight. Hum Reprod 2010;25:1123–6.
126. Rai R, Backos M, Rushworth F, Regan L. Polycystic ovaries and recurrent miscarriage—a reappraisal. Hum Reprod 2000;15:612–5.
127. Fedorcsák P, Storeng R, Dale PO, Tanbo TOM, Åbyholm T. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta Obstet Gynecol Scand 2000;79:43–8.
128. Al-Biate MaS. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. Taiwan J Obstet Gynecol 2015;54:266–9.
129. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:524–9.
130. Khattab S, Fotouh IA, Mohesn IA, Metwally M, Moaz M. Use of metformin for prevention of ovarian hyperstimulation syndrome: a novel approach. Reprod Biomed Online 2006;13:194–7.
131. Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages, and beneficial effect of metformin in these patients: a prospective clinical study. Fertil Steril 2008;90:727–30.
132. Zhao Q, He J. Efficacy and safety of metformin in pregnant women with polycystic ovary syndrome: a systematic review with meta-analysis of randomized and non-randomized controlled trials. Gynecol Endocrinol 2022;38:558–68.
133. Hanem LGE, Salvesen Ø, Juliusson PB, Carlsen SM, Nossum MCF, Vaage M, et al. Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5-10 year follow-up of the PregMet randomised controlled trial. Lancet Child Adolesc Health 2019;3:166–74.
134. Andrade C. Major malformation risk, pregnancy outcomes, and neurodevelopmental outcomes associated with metformin use during pregnancy. J Clin Psychiatry 2016;77:e411–4.
135. Bussen S, Sütterlin M, Steck T. Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. Hum Reprod 1999;14:18–20.
136. Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril 1998;70:246–52.

137. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A Randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med 2015;373:2141–8.
138. Stephenson MD, McQueen D, Winter M, Kliman HJ. Luteal start vaginal micronized progesterone improves pregnancy success in women with recurrent pregnancy loss. Fertil Steril 2017;107:684–90.e2.
139. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med 2019;380:1815–24.
140. Jacobs PA, Hassold TJ, editors. Chromosome abnormalities: origin and etiology in abortions and livebirths. Berlin Heidelberg: Springer; 1987:233–44.
141. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril 2018;109:429–36.
142. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod 2016;31:1668–74.
143. Bhatt SJ, Marchetto NM, Roy J, Morelli SS, Mcgovern PG. Pregnancy outcomes following in vitro fertilization frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) in women with recurrent pregnancy loss (RPL): a SART-CORS study. Hum Reprod 2021;36:2339–44.
144. Mumusoglu S, Telek SB, Ata B. Preimplantation genetic testing for aneuploidy in unexplained recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2025;123:121–6.
145. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Electronic address: asrm@asrm.org. The use of preimplantation genetic testing for aneuploidy: a committee opinion. Fertil Steril 2024;122:421–34.
146. Shehata H, Ali A, Silva-Edge M, Haroon S, Elfituri A, Viswanatha R, et al. Thrombophilia screening in women with recurrent first trimester miscarriage: is it time to stop testing? - a cohort study and systematic review of the literature. Br Med J Open 2022;12:e059519.
147. Quenby S, Farquharson RG, Dawood F, Hughes AM, Topping J. Recurrent miscarriage and long-term thrombosis risk: a case–control study. Hum Reprod 2005;20:1729–32.
148. Kaandorp SP, Goddijn M, Van Der Post JaM, Hutten BA, Verhoeve HR, Hamulyák K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010;362:1586–96.
149. Giancotti A, Torre RL, Spagnuolo A, D'ambrosio V, Cerekja A, Piazze J, et al. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. J Matern Fetal Neonatal Med 2012;25:1191–4.
150. Li J, Gao YH, Xu L, Li ZY. Meta-analysis of heparin combined with aspirin versus aspirin alone for unexplained recurrent spontaneous abortion. Int J Gynaecol Obstet 2020;151:23–32.
151. De Jong PG, Quenby S, Bloemenkamp KWM, Braams-Lisman BaM, De Bruin JP, Coomarasamy A, et al. ALIFE2 study: low-molecular-weight heparin for women with recurrent miscarriage and inherited thrombophilia–study protocol for a randomized controlled trial. Trials 2015;16:208.
152. Yan X, Wang D, Yan P, Li H. Low molecular weight heparin or LMWH plus aspirin in the treatment of unexplained recurrent miscarriage with negative antiphospholipid antibodies: a meta-analysis of randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2022;268:22–30.
153. Atasever MMD, Soyman ZMD, Demirel EMD, Gencdal SMD, Kelekci SMD. Diminished ovarian reserve: is it a neglected cause in the assessment of recurrent miscarriage? A cohort study. Fertil Steril 2016;105:1236–40.
154. Bunnewell SJ, Honess ER, Karia AM, Keay SD, Al Wattar BH, Quenby S. Diminished ovarian reserve in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2020;113:818–27.e3.
155. Leclercq E, De Saint Martin L, Bohec C, Le Martelot MT, Roche S, Alavi Z, et al. Blood anti-Müllerian hormone is a possible determinant of recurrent early miscarriage, yet not conclusive in predicting a further miscarriage. Reprod Biomed Online 2019;39:304–11.
156. Murugappan G, Shahine L, Lathi RB. Antimullerian hormone is a predictor of live birth in patients with recurrent pregnancy loss. Fertil Res Pract 2019;5: 2–2.
157. Wald KA, Shahine LK, Lamb JD, Marshall LA, Hickok LR. High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients. Gynecol Endocrinol 2020;36:1079–81.
158. Lyttle Schumacher BM, Jukic AMZ, Steiner AZ. Antimüllerian hormone as a risk factor for miscarriage in naturally conceived pregnancies. Fertil Steril 2018;109:1065–71.e1.
159. Zarek SM, Schisterman EF, Mitchell EM, Silver RM, Segars JH, Mumford SL. Association of anti-mullerian hormone (AMH) and pregnancy loss. Fertil Steril 2014;102: e270–e270.
160. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Tobacco or marijuana use and infertility: a committee opinion. Fertil Steril 2024;121:589–603.
161. Lassi ZS, Imam AM, Dean SV, Bhutta ZA. Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure. Reprod Health 2014;11:S6.
162. Lindbohm M-L, Sallmén M, Taskinen H. Effects of exposure to environmental tobacco smoke on reproductive health. Scand J Work Environ Health 2002;28:84–96.
163. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2014;179:807–23.
164. Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, Van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr 2016;19:1233–44.
165. Ng KYB, Cherian G, Kermack AJ, Bailey S, Macklon N, Sunkara SK, et al. Systematic review and meta-analysis of female lifestyle factors and risk of recurrent pregnancy loss. Sci Rep 2021;11:7081.
166. Stefanidou EM, Caramellino L, Patriarca A, Menato G. Maternal caffeine consumption and sine causa recurrent miscarriage. Eur J Obstet Gynecol Reprod Biol 2011;158:220–4.
167. Schlüssel MM, Souza EB, Reichenheim ME, Kac G. Physical activity during pregnancy and maternal-child health outcomes: a systematic literature review. Cad Saude Publica 2008;24(Suppl 4):s531–44.
168. Cavalcante MB, Sarno M, Peixoto AB, Araujo Júnior E, Barini R. Obesity and recurrent miscarriage: a systematic review and meta-analysis. J Obstet Gynaecol Res 2019;45:30–8.
169. Sugiura-Ogasawara M. Recurrent pregnancy loss and obesity. Best Pract Res Clin Obstet Gynaecol 2015;29:489–97.
170. Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Hum Reprod 2015;30:777–82.
171. Li W, Newell-Price J, Jones GL, Ledger WL, Li TC. Relationship between psychological stress and recurrent miscarriage. Reprod Biomed Online 2012;25:180–9.
172. Voss P, Schick M, Langer L, Ainsworth A, Ditzen B, Strowitzki T, et al. Recurrent pregnancy loss: a shared stressor—couple-orientated psychological research findings. Fertil Steril 2020;114:1288–96.
173. Qu F, Wu Y, Zhu YH, Barry J, Ding T, Baio G, et al. The association between psychological stress and miscarriage: A systematic review and meta-analysis. Sci Rep 2017;7:1731.
174. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 1997;12:387–9.