Evaluation of Recurrent Pregnancy Loss

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Recurrent pregnancy loss (RPL) affects approximately 5% of couples. Although RPL definitions vary across professional societies, an evaluation after a second clinically recognized first-trimester pregnancy loss is recommended. Good quality evidence links parental chromosomal rearrangements, uterine anomalies, and antiphospholipid syndrome (APS) to RPL. In contrast, the relationship between RPL and other endocrine, hematologic, and immunologic disorders or environmental exposures is less clear. Anticoagulant therapy and low-dose aspirin are recommended for patients with RPL who have also been diagnosed with APS. Vaginal progesterone supplementation may be considered in patients experiencing vaginal bleeding during the first trimester. Surgical correction may be considered for patients with RPL in whom a uterine anomaly is identified. Evaluation and management of additional comorbidities should be guided by the patient’s history rather than solely based on the diagnosis of RPL, with the goal of improving overall health to reduce complications in the event of pregnancy. Most people with RPL, including those without identifiable risk factors, are expected to achieve a live birth within 5 years from the initial evaluation. Nevertheless, clinicians should be sensitive to the psychological needs of individuals with this condition and provide compassionate and supportive care across all stages.

Approximately 50% of all pregnancies end at the preclinical stage due to biochemical loss or implantation failure. Among pregnancies recognized clinically, one in every five is expected to end in pregnancy loss. The overall prevalence of recurrent pregnancy loss (RPL) is approximately 5%. For these patients, an etiology is identified in 50% of cases and the risk of pregnancy loss in a subsequent pregnancy increases with the number of prior losses (3.9%, 6.5%, and 9% recurrence risk for two, three, and four prior losses, respectively), sharply increasing after six losses. Furthermore, population-based studies have found that siblings of patients with RPL have a higher frequency of pregnancy losses than the general population. Fortunately, about two-thirds of people with RPL who continue to attempt pregnancy are expected to achieve a live birth within 5 years of the initial workup, regardless of prior medical intervention.

DEFINITIONS AND TERMINOLOGY

There is a lack of consensus about the definitions of RPL among the leading international societal guidelines (Table 1). However, the degree to which a standardized broader compared with more specific definition would make a significant difference in estimated prevalence or anticipated subsequent live-birth rate is not well defined. Limited evidence suggests that neither the number nor the consecutive compared with nonconsecutive nature of pregnancy losses significantly affects the strength of association between RPL and known risk factors. In contrast, one observational study found that patients with unexplained RPL experiencing consecutive pregnancy losses have a poorer
prognosis than their counterparts. Nonetheless, clinicians are encouraged to use their clinical discretion and may recommend medical evaluation after two first-trimester pregnancy losses if there is a suspicion that they are pathologic and not sporadic in nature.

CAUSES

The causes of RPL can be categorized broadly into genetic errors, uterine structural abnormalities, and clotting disorders. In other cases, the cause is found to be multifactorial, associated with underlying medical conditions, or unknown. More than half of pregnancy losses result from random numeric cytogenic errors. Age-associated pregnancy loss is driven mainly by this phenomenon, and the incidence of pregnancy loss increases with maternal age, from approximately 4% for individuals younger than age 20 years to approximately 20% for those older than age 35 years and more than 50% for those older than age 42 years. Whole chromosome nondisjunction events are preferentially associated with increased instances of aneuploidy in young individuals, whereas centromeric and more extensive cohesion loss limit fertility in older patients. These abnormalities preclude further development and breakdown of the fetal-maternal interface, resulting in bleeding, cramping, and pregnancy loss.

In patients with RPL, genetic anomalies, including parental cytogenetic abnormalities and single-gene disorders, are detected in 2–5% cases. Additional etiologies include structural uterine anomalies, such as arcuate, septate, unicornuate, bicornuate, and Didelphis uteri. Similarly, antiphospholipid syndrome (APS) is found in up to 1–20% of patients with RPL (Fig. 1).

WORKUP

In this review, we recommend evaluation and management strategies for patients with two or more early pregnancy losses regardless of the sequence of the losses (Box 1). Any evaluation should begin with a thorough history and relevant physical examination, including obtaining and reviewing any records such as ultrasound reports, human chorionic gonadotropin levels, previous laboratory test results, and pathology reports. Genetic counseling should be offered when available.
GENETIC

Products of Conception Testing
We recommend that genetic testing of the products of conception with single-nucleotide polymorphism (SNP) microarray be offered by the obstetrician–gynecologist to all patients as soon as pregnancy loss is confirmed, including with the first occurrence for second-trimester losses and the second occurrence or beyond for first-trimester losses.

Sugiura et al evaluated 1,676 individuals with RPL, 69% of which were unexplained after negative test results for antiphospholipid antibodies, transvaginal ultrasonography and hysterosalpingography, testing for hypothyroidism and diabetes, and chromosomal analysis of both partners. Their group evaluated the products of conception with traditional karyotype testing and found that 41% of the pregnancy losses that were thought to be unexplained had abnormal karyotypes.30 Foyouzi et al31 suggested that products of conception testing becomes cost effective starting with the second pregnancy loss.

Karyotype testing of the products of conception requires viable cells, which can be cultured in the laboratory. Unfortunately, this is often not feasible in the setting of pregnancy loss. Additionally, maternal cell contamination may confound the results. Therefore, SNP microarray typically is recommended for products of conception genetic analysis. Microarray assesses the relative amount of genetic material present in the sample. Compared with traditional karyotyping, this method has a faster turnaround time, higher resolution (less than 100 kb), and can detect maternal cell contamination and uniparental disomy. Additionally, it can be used on paraffin-embedded blocks to test pathologic specimens from prior losses, making SNP microarray a more effective and cost-efficient testing modality. Of note, the SNP microarray is unable to detect balanced translocations. However, this type of genetic change is not expected to lead to pregnancy loss. Thus, this limitation may not be clinically relevant.32

Whole exome sequencing and whole genome sequencing have shown potential to identify additional genetic causes of RPL.30 However, the cost of these technologies continues to be limiting. It is important to note that, although genetic testing may be able to identify a presumed cause of a pregnancy loss, there is not typically anything modifiable to avoid future pregnancy loss. Patients should therefore be counseled that the main goal of genetic testing is to try to identify a cause of that specific pregnancy loss.

Parental Testing
For couples with RPL, we recommend offering parental karyotyping, especially for cases in which previous products of conception testing results showed unbalanced structural chromosomes or translocations, or when products of conception results are not available.2,33

Parental balanced translocations increase the risk of unbalanced translocation affecting the offspring. Approximately 2–4% of couples with RPL have chromosomal rearrangements. Traditional karyotyping is the modality of choice for parental testing to screen for balanced translocations.

The overall live-birth rate of translocation carriers is 71% without assisted reproductive technology.30–32,34–36 Given the high live-birth rate without intervention and the low prevalence of balanced translocations, the utility of testing has been called into question. Accordingly, recommendations regarding parental evaluation vary across societal guidelines. Specifically, although the American Society for Reproductive Medicine (ASRM) and the American College of Obstetricians and Gynecologists (ACOG) favor testing in couples with RPL, the ESHRE (European Society of Human Reproduction and Embryology) recommends against it.2,34,37

ENDOCRINE

Thyroid Disorders
We recommend assessment of thyroid function in patients with RPL.

Overt Hypothyroidism
For patients with overt hypothyroidism, we recommend supplementation with levothyroxine irrespective of RPL diagnosis.

Overt hypothyroidism is defined as an elevated thyroid-stimulating hormone (TSH) level and a decreased free thyroxine (FT4) level, according to trimester-specific reference ranges, or a serum TSH level of 10 milliunits/L or higher.38 The American Thyroid Association’s guidelines recommend that, if thyroid function is assessed during pregnancy, population- and trimester-specific reference ranges for serum TSH levels should be used for the diagnosis and management of thyroid disease during pregnancy.38

Studies examining the association between RPL and overt hypothyroidism are limited. Some studies...
have suggested that patients with RPL have a higher incidence of hypothyroidism than patients in a control group (4.29% vs 0.61%). Conversely, others found no significant differences in RPL rates when comparing overtly hypothyroid with euthyroid patients.\textsuperscript{39,40} Nonetheless, normal maternal thyroid levels are critical for embryonic, fetal, and neurocognitive development.\textsuperscript{41}

**Subclinical Hypothyroidism and Thyroid Peroxidase Antibody Status**

For patients with RPL, we recommend discussing the risks and benefits of levothyroxine supplementation with patients with subclinical hypothyroidism or based on thyroid peroxidase (TPO) antibody status due to limited evidence showing improved live-birth rate.

The American Thyroid Association and ACOG define subclinical hypothyroidism as elevated serum TSH levels and normal serum FT\textsubscript{4} levels.\textsuperscript{38,42}

In a systematic review, Vissenberg et al\textsuperscript{43} suggested that altered thyroid hormone levels and the presence of circulating TPO antibodies were associated with disturbed fertilization and embryogenesis. Furthermore, Liu et al demonstrated a graded increase in pregnancy loss risk with higher maternal serum TSH levels. The risk was highest in the subset of patients who tested positive for TPO antibodies.\textsuperscript{44} This phenomenon may be related to an increased incidence of overt hypothyroidism over time in this subset of patients.\textsuperscript{38}

Studies on the association between RPL and subclinical hypothyroidism have yielded conflicting results. Triggianese et al\textsuperscript{45} suggested a link between subclinical hypothyroidism and RPL in patients with consecutive pregnancy losses. However, such a link has not been demonstrated for couples with nonconsecutive pregnancy losses. Furthermore, treatment with levothyroxine has failed to improve live-birth rates for both euthyroid patients with thyroid antibodies and patients with subclinical hypothyroidism.\textsuperscript{45–47}

The 2023 ESHRE guidelines state that, “a clear association between thyroid autoimmunity and RPL has been found,” and therefore recommend screening with TSH and TPO antibodies for all women with RPL.\textsuperscript{2} The 2017 American Thyroid Association guidelines state that there is weak evidence supporting a possible benefit of administration of levothyroxine to pregnant euthyroid women with TPO antibodies.\textsuperscript{38} This evidence is not addressed in the ACOG document about thyroid disease in pregnancy. We recommend that health care professionals discuss with patients the available evidence on levothyroxine administration in the setting of subclinical hypothyroidism, positive TPO antibodies, and RPL and decide on treatment using a shared decision-making model.

**Hyperthyroidism**

We recommend adhering to American Thyroid Association guidelines for management of hyperthyroidism regardless of miscarriage history.

We recommend against treatment for subclinical hyperthyroidism in patients with RPL.

Overt hyperthyroidism is defined as a suppressed or undetectable serum TSH level and abnormally high serum total thyroxine/FT\textsubscript{4} or free triiodothyronine levels. Pregnancy complications such as spontaneous pregnancy loss, preeclampsia, preterm birth, and heart failure are associated with this condition. In contrast, the association between overt hyperthyroidism and RPL is not well-established. However, given the rates of adverse pregnancy outcomes in patients with uncontrolled hyperthyroidism, we recommend optimization of this condition prepregnancy. In contrast, subclinical hyperthyroidism, defined as a suppressed TSH level with a normal FT\textsubscript{4} level, has been associated with neither RPL nor adverse pregnancy outcomes and does not need to be treated.

**Progesterone**

We do not recommend assessment of progesterone level in patients with RPL.

The corpus luteum secretes progesterone and supports the pregnancy during the first trimester. Luteal phase deficiency refers to a decreased level of progesterone secretion during the implantation window, 5–10 days after the surge in luteinizing hormone. Proposed causes include inadequate progesterone production by the corpus luteum, stress, exercise, weight loss, hyperprolactinemia, and perimenopause.\textsuperscript{48,49} About 35% of women with RPL have some form of luteal phase abnormality.\textsuperscript{23} However, there is no good way to ascertain whether there is a luteal phase deficiency, and progesterone therapy is not recommended for treatment of RPL.

We recommend consideration of supplementation with progesterone in patients with early pregnancy bleeding and RPL, because it may decrease the risk of miscarriage.\textsuperscript{50–52}

In patients with RPL without early pregnancy bleeding, we do not recommend giving progesterone.\textsuperscript{53,54}

There is high-quality evidence demonstrating that beginning progesterone support at the time of recognition of pregnancy does not alter live-birth rates; therefore, we do not recommend beginning...
progesterone supplementation after a documented positive human chorionic gonadotropin test result.\textsuperscript{54} One area of controversy is among pregnancies in patients with RPL who have onset of bleeding. There have been several studies evaluating this specific clinical circumstance,\textsuperscript{50–52} and these indicate a potential benefit for progesterone support to prevent pregnancy loss in this population. If progesterone supplementation is selected in patients with RPL who experience bleeding in the first trimester, we recommend vaginal micronized progesterone, 400 mg twice daily.

**Prolactin**

*We do not recommend evaluation for hyperprolactinemia or hypoprolactinemia in patients with RPL due to insufficient data supporting testing.*

Hyperprolactinemia is the most common hypothalamic-pituitary dysfunction. Elevated prolactin levels cause ovulatory dysfunction and menstrual disorders. Brain magnetic resonance imaging is the modality of choice to rule out sellar masses in patients with clinical symptoms after ruling out other causes. High prolactin levels (more than 100 ng/mL) inhibit granulosa cell progesterone secretion in vitro,\textsuperscript{55} highlighting a potential role of hyperprolactinemia in luteal phase defects. A correlation between hyperprolactinemia and sex hormone inhibition has been shown in patients with infertility and RPL. There are conflicting studies regarding the role of prolactin levels in RPL, with some indicating an association between abnormal prolactin levels and RPL and others showing no association at all. Routine testing of prolactin levels cannot be recommended for all patients with RPL.

**Diabetes Mellitus**

*We do not recommend that patients with RPL be screened for diabetes unless they have clinical indications for screening.*

Patients with well-controlled insulin-dependent diabetes mellitus have RPL rates similar to those in the general population.\textsuperscript{56} Enhanced glycemic control also improves pregnancy outcomes.\textsuperscript{57,58} In contrast, poorly controlled diabetes in the periconceptional period increases the risk of hyperglycemia-induced lethal embryonic malformations.\textsuperscript{59} Therefore, we recommend optimization of glycemic control for patients with diabetes during the preconception period, with a goal of hemoglobin A\textsubscript{1C} levels less than 6.5%. In patients with unexplained RPL and without symptoms or risk factors for diabetes, there is no evidence to support screening.\textsuperscript{60}

**Polycystic Ovarian Syndrome**

*We recommend that decisions about treating polycystic ovarian syndrome (PCOS) and insulin resistance be made according to accepted guidelines and not altered due to a concurrent diagnosis of RPL.*

Studies have aimed to investigate the relationship among PCOS, insulin resistance, and RPL.\textsuperscript{61} There is consistent evidence that patients with RPL who have PCOS have a higher rate of subsequent miscarriage than patients with RPL without PCOS.\textsuperscript{62–64} Previous authors have described improved pregnancy outcomes in patients with PCOS or insulin resistance treated with metformin.\textsuperscript{18,65,66} However, this benefit is not well-established with respect to prevention of recurrent miscarriage.

**STRUCTURAL**

**Uterine Abnormalities**

*We recommend evaluation of the uterine cavity as a component of the workup for RPL.*

Studies have shown that congenital uterine structural abnormalities such as arcuate, septate, unicornuate, bicornuate, and didelphis uteri are more prevalent in individuals who experience miscarriage than in the general population.\textsuperscript{67} Canalization defects, such as the septate uterus, have the highest association with RPL; patients with these defects have significantly increased rates of late first-trimester miscarriages compared with individuals with unexplained RPL.\textsuperscript{5,68} The link between structural anomalies and RPL is not fully understood. Some groups have postulated that patients with canalization defects have endometrium overlying the septum, which is abnormally vascularized, leading to suboptimal implantation.\textsuperscript{69} In contrast, evidence supporting a potential link between acquired structural uterine abnormalities (submucosal myomas, endometrial polyps, and intrauterine adhesions) and RPL is contradictory.\textsuperscript{6}

Several modalities are available to diagnose structural uterine abnormalities. A pooled analysis of 38 studies showed that three-dimensional ultrasonography had the highest overall diagnostic accuracy for uterine anomalies (97.6%), followed by hysterosalpingography (86.9%) and two-dimensional ultrasonography (86.6%). Magnetic resonance imaging had a diagnostic accuracy higher than 90%. However, the latter typically is reserved for challenging cases associated with complex anatomical defects.\textsuperscript{9} Hysteroscopy or saline infusion sonohysterography may help assess the uterine cavity for defects affecting the endometrial lining. Studies have demonstrated the improved accuracy of saline infusion sonohysterography over conventional transvaginal
ultrasonography in the detection of myomas, polyps, and intrauterine adhesions.\textsuperscript{70,71}

There is a lack of consensus in the literature regarding the surgical management of congenital and acquired uterine abnormalities. We recommend imaging the uterus during evaluation for RPL with either saline infusion sonohysterography combined with three-dimensional ultrasonography or hysterosalpingography. In patients with abnormal findings, this can be followed by hysteroscopy for confirmation and subsequent surgical correction of defects such as polyps, submucous myomas, intrauterine adhesions, and septae. Resection of these defects has been demonstrated to improve live-birth rates.\textsuperscript{72,73}

HEMATOLOGIC

Antiphospholipid Syndrome

We recommend testing for the laboratory features of APS (lupus anticoagulant, anticardiolipin immunoglobulin [IgG and IgM], and anti-beta-2-glycoprotein I IgG and IgM) in patients with RPL.

We do not recommend testing for other antiphospholipid antibodies.

We recommend treatment with aspirin and heparin in patients who meet clinical and laboratory criteria for APS and who are diagnosed with RPL.

We do not recommend anticoagulation (heparin or aspirin) for the treatment of RPL in the absence of APS.

In addition to RPL, APS is associated with thromboembolic events, preeclampsia, preterm birth, fetal growth restriction, and stillbirth.\textsuperscript{74} Antiphospholipid syndrome is a rare acquired thrombophilia, with an overall prevalence of 50 per 100,000 individuals.\textsuperscript{75} The diagnosis is made based on a combination of clinical and laboratory criteria (Table 2). Approximately 1–5% of the general healthy population has antiphospholipid antibodies, which are immunoglobulins directed against proteins attached to phospholipids.\textsuperscript{76,77} A systematic review reported that 6% of patients with antiphospholipid antibodies have RPL;\textsuperscript{29} other studies have reported the frequency to be 15–20%.\textsuperscript{28} A more recent retrospective cohort study found that the prevalence of APS in patients with RPL is similar to that in the general population, at approximately 1%.\textsuperscript{27}

The variation in reported prevalence of APS among patients with RPL is likely due to limitations in the studies, such as variation in the diagnostic criteria used for both RPL and APS, different commercial kits available for antiphospholipid antibody testing that lead to lack of interlaboratory reproducibility, and heterogeneity of antibodies tested, along with inclusion of individuals with weak or low positive antibody test results.\textsuperscript{29,78}

Currently, there is a debate as to whether there is an association between the presence of antiphospholipid antibodies and RPL, in particular the use of anti-beta-2-glycoprotein-I as part of the defined laboratory criteria.\textsuperscript{79} However, both the ASRM\textsuperscript{33} and ACOG\textsuperscript{26} guidelines recommend testing for antiphospholipid antibodies. The ESHRE\textsuperscript{2} and Royal College of Obstetricians and Gynaecologists\textsuperscript{17} guidelines do as well, with emphasis on testing for lupus anticoagulant and anticardiolipin antibodies, and potentially also including anti-beta-2-glycoprotein-I antibodies but not required.

Lupus anticoagulant was associated with adverse pregnancy outcomes in a study evaluating patients with inactive or stable active systemic lupus erythematosus compared with patients who were seronegative, regardless of treatment.\textsuperscript{80} Anticardiolipin is the most common sole antibody present in patients with APS; patients with anti-beta-2-glycoprotein-I antibodies have been reported to have the highest incidence of thrombotic events, late adverse pregnancy outcomes, and lowest birth rates in some studies.\textsuperscript{79,81,82} However, a meta-analysis in 2021 evaluated six prospective studies, two of which focused on thrombotic outcomes and the other four on obstetric outcomes.\textsuperscript{83} Two studies identified an association between IgG anti-beta-2-glycoprotein-I and thrombosis.\textsuperscript{83} Three of the four studies evaluating obstetric outcomes did not find an association between anti-beta-2-glycoprotein-I antibodies and adverse pregnancy outcomes.\textsuperscript{83} Further studies are needed to clarify the clinical relevance of anti-beta-2-glycoprotein I antibodies.

Broadly, the live-birth rate for patients diagnosed with APS with lupus anticoagulant, anticardiolipin antibody, anti-beta-2-glycoprotein-I antibody, double positive and lupus anticoagulant negative, and triple positive has been reported as 79.6%, 56.3%, 47.7%, 43.3%, and 30.0%, respectively, despite therapy.\textsuperscript{81} Individuals with multiple antibody-positive results have lower live-birth rates compared with those with a single positive result.

Treatment guidelines recommend a combination of prophylactic heparin (unfractionated heparin 7,500 units/d or low-molecular-weight heparin 40 mg/d) and low-dose aspirin 50–100 mg/d for patients with APS and no history of thrombosis.\textsuperscript{84–86} Those with a history of thrombosis typically are treated with full (therapeutic) anticoagulation dose (low-molecular-weight heparin 1 mg/kg twice a day).\textsuperscript{79} In patients with RPL, low-dose
aspirin should be started either before pregnancy or in combination with prophylactic heparin after a positive pregnancy test. A retrospective single-center cohort study evaluated pregnancy outcomes in patients with antiphospholipid antibodies who were treated with hydroxychloroquine, and the results showed a higher rate of live births and lower prevalence of antiphospholipid antibody–related pregnancy morbidity with hydroxychloroquine use. Currently, there are three ongoing clinical trials (EudraCT 2016-002256-25, NCT04275778, NCT03540810) evaluating the efficacy of hydroxychloroquine in the prevention of RPL. Some experts advocate for the use of hydroxychloroquine (200–400 mg/d) in patients with RPL who are lupus anticoagulant–positive; however, data are limited and more studies are needed to determine the utility of hydroxychloroquine in patients with RPL and lupus anticoagulant–positive antibodies.

**Inherited Thrombophilias**

We do not recommend testing for inherited thrombophilia as part of the workup for RPL.

The ACOG, ASRM, and ESHRE guidelines recommend against inherited thrombophilia testing in the setting of RPL. There is not a consistent association between inherited thrombophilias (factor V Leiden homozygosity, prothrombin gene G2010A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G 20210A mutation or antithrombin, protein C, protein S deficiency) and RPL in the literature.

**Immunologic Factors**

We do not recommend testing for human leukocyte antigen, multiantigen immunoassays, or antinuclear antibodies (ANA) in the setting of RPL. We do not recommend the use of steroids, intravenous immunoglobulins, filgrastim (a cytokine growth factor), intralipids, or paternal lymphocyte immunotherapy for unexplained RPL until clear clinical data supporting their use are available.

Studies in reproductive immunology have suggested disruption of maternal immune tolerance as a possible cause of RPL. Maternal immune cells make up almost half of the first-trimester decidual cells and undergo modulation before and after implantation to assure tolerance of the fetal cells, which behave as a semi-allogenic graft to the maternal immune system. The maternal immune system paradoxically accepts and tolerates the semi-allogenic fetus, recognizes the fetal antigens, and actively diverges to a protective response. Multiple studies have attempted to demonstrate a causal link between immunologic factors and RPL. Although there has been some progress in the area, the next steps to translational science and clinical studies evaluating potential immune-modulating interventions are lacking or are not robust. Potential therapeutic targets include IgG, steroids, and intralipids or infusions such as paternal lymphocyte immunotherapy. The effectiveness of these therapies remains to be demonstrated through appropriate trials with strict inclusion criteria. Although some international trials have shown a

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Table 2. 1999 Sapporo Criteria for Diagnosis of Antiphospholipid Syndrome

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<tr>
<th>Clinical Criteria for APS*</th>
<th>Laboratory Criteria for APS†</th>
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<tr>
<td>Vascular thrombosis</td>
<td>1. Lupus anticoagulant present in plasma, or</td>
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<tr>
<td>a) Arterial, or</td>
<td>2. Anticardiolipin antibody IgG/IgM isotype present in medium or high titer (greater than 40 GPL or MPL or greater than the 99th percentile), or</td>
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<td>b) Venous, or</td>
<td>3. Anti-beta-2-glycoprotein I antibody IgG or IgM isotype (titer greater than the 99th percentile) present in either plasma or serum and tested by standardized ELISA.</td>
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<td>c) Small vessel, or</td>
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<td>Pregnancy morbidity</td>
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<td>a) 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or</td>
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<td>b) 1 or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia, or severe preeclampsia, or recognized features of placental insufficiency, or</td>
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<tr>
<td>c) 3 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.</td>
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Ig, immunoglobulin; ELISA, enzyme-linked immunosorbent assay.

* Only one of the listed clinical criteria is needed in conjunction with laboratory testing for diagnosis.
† Laboratory criteria must be present on two or more occasions at least 12 weeks apart.
More recently, there is insufficient evidence to date showing benefit from IVF in RPL. Fertility treatments in fertile patients with RPL are unlikely to significantly improve the chances of achieving an ongoing pregnancy within 6 months of a negative workup, including IVF with preimplantation genetic screening. Therefore, patients with RPL should be encouraged regarding the high rates of fertility and the likelihood of success with attempts at spontaneous conception for at least 6 months. Studies evaluating IVF with preimplantation genetic screening compared with expectant management have not shown a shortened time to next pregnancy for couples with unexplained RPL. Given the lack of clinical studies, we recommend reserving IVF for couples with RPL and secondary subfertility until more data become available.

ENVIRONMENTAL

Obesity

We recommend providing support through a multidisciplinary approach for weight loss.

Studies have demonstrated that increasing body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) correlates with increasing risk of spontaneous pregnancy loss in women who conceive spontaneously. Obesity is thought to cause reproductive dysfunction through insulin resistance and hyperandrogenism. A meta-analysis of studies evaluating women with BMIs higher than 25 compared with those with BMIs in the normal range in the general population noted benefit of lymphocyte immunotherapy, this therapy is not approved for use in the United States. Steroid treatment was shown to improve live-birth outcomes in patients with RPL in a recent meta-analysis. However, the studies included were inadequately powered, had co-intervention with heparin and aspirin, and had notable heterogeneity in inclusion criteria. It is unclear whether prednisone improves outcomes for patients with RPL. Furthermore, its use is associated with an increased risk of prematurity, gestational diabetes mellitus, and hypertension. There is an ongoing clinical trial (PREMI trial, NCT05725512) evaluating the effects of prednisolone on unexplained RPL.

More studies are needed to ascertain whether there are clinical benefits of alternative treatment modalities, such as intravenous Ig and filgrastim, for the treatment of RPL. Some studies have evaluated other maternal antibodies, such as ANA in patients with unexplained RPL; however, the role of these antibodies has been controversial. More recently, a meta-analysis evaluating 22 studies showed a statistically significantly higher risk of RPL, more than threefold higher, in patients who were ANA-positive compared with those who were ANA-negative. Subgroup analysis in the same study, considering the different definitions for RPL, confirmed the cumulative data, suggesting that the effect is present irrespective of the definition used for RPL. Studies have evaluated the use of prednisone in patients with positive ANA titers, but the results have been inconclusive. As such, more studies are needed to elucidate the effect of immunomodulatory therapies in patients with positive ANA titers and RPL.

ASSISTED REPRODUCTIVE TECHNOLOGY

We do not recommend assisted reproductive technology for management of RPL.

We recommend reserving in vitro fertilization (IVF) for couples with RPL and secondary subfertility.
the odds of RPL to be significantly higher in women with overweight.\textsuperscript{117} Within the population with RPL, the odds of having a subsequent miscarriage were significantly higher in groups with BMIs higher than 30 and higher than 25 compared with those with BMIs in the normal range.\textsuperscript{117} However, the quality of the data was low because the studies were all observational. Thus, further studies are needed to determine whether weight loss improves live-birth rates in patients with RPL who have obesity or overweight. Given the multiple health benefits of weight loss, we encourage a multidisciplinary approach to support these individuals in achieving normal-range BMIs when possible.

Caffeine, Tobacco, and Alcohol

We recommend counseling patients on optimizing environmental factors that may affect pregnancy outcome.

We recommend providing support through a multidisciplinary approach for smoking cessation and alcohol abstinence periconception and during pregnancy.

Excessive caffeine intake, alcohol exposure, and tobacco use all have been linked to an increased risk of miscarriage. The risk of RPL is dose-dependent for alcohol, tobacco, and caffeine use.\textsuperscript{117,118} Risk of miscarriage with tobacco exposure appears to be modified by maternal age. Farioli et al reported that, in individuals aged 25–29 years, miscarriage risk was not associated with tobacco smoke exposure, whereas all other age classes presented a higher risk of miscarriage in the presence of active smoking.\textsuperscript{119–121} A meta-analysis evaluating five studies on smoking and RPL reported increased risk of miscarriage with cigarette smoking, with one study showing a significant association between second-hand cigarette smoke and miscarriage. However, the quality of the evidence for the associations between smoking and RPL risk was very low because of inconsistency of results across the small number of studies included.\textsuperscript{117} Smoking cessation and alcohol abstinence have additional health benefits; therefore, cessation is encouraged for patients attempting to conceive.\textsuperscript{120,121}

A meta-analysis evaluating caffeine intake and its association with RPL showed higher odds of RPL in women consuming more than 99 mg/d of caffeine than in those consuming less than 99 mg/d; however, the findings were not statistically significant.\textsuperscript{117} The highest risk of RPL is for patients consuming more than 300 mg/d of caffeine. Therefore, patients should limit their caffeine intake to less than 300 mg/d and consider further limitation to less than 99 mg/d.\textsuperscript{117,119–123}

OTHER

Vitamin D Deficiency

We do not recommend screening for vitamin D deficiency as part of the RPL workup.

We recommend treatment with vitamin D for patients who are deficient to optimize their overall health.

Vitamin D is a known immune modulator. Deficiencies in vitamin D have been linked to increased autoantibody levels and higher disease activity in patients with autoimmune conditions that may indirectly predispose them to higher rates of miscarriage.\textsuperscript{124–126}

Although vitamin D deficiency is commonly treated in patients who are trying to conceive,\textsuperscript{124,127} evidence to support a clear association between vitamin D deficiency and RPL is lacking.\textsuperscript{124,127} as is evidence showing improved live-birth rates in patients with RPL after supplementation.\textsuperscript{128}

Male Factors Contributing to Recurrent Pregnancy Loss

We do not recommend semen analysis for couples with RPL.

Male partners of women with RPL are reported to have significantly higher rates of sperm DNA fragmentation than partners of fertile women in a control group.\textsuperscript{129,130} Decreased sperm global methylation levels and aberrant sperm methylation patterns in imprinted genes such as \textit{IGF2-H19 DMR}, IG-DMR, MEST, ZAC, KcDMR, PEG10, and PEG3 have been associated with RPL.\textsuperscript{131} However, there is a lack of robust data to suggest any viable intervention to mitigate these risks, and further studies are necessary before implementation of screening for semen abnormalities in clinical practice.

Infections

We do not recommend performing endometrial biopsy for the purpose of evaluating RPL.

Studies assessing the role of acute and chronic infection in RPL have yielded inconsistent results.\textsuperscript{132} Cao et al\textsuperscript{133} found higher rates of infection with \textit{Ureaplasma urealyticum} or \textit{Mycoplasma hominis} in the chorion and decidua of patients with RPL. However, follow-up studies have yet to be able to replicate those results. Therefore, further research is needed before making recommendations in this regard.

Chronic endometritis is a persistent inflammation of the endometrial lining that may present with abnormal uterine bleeding, pelvic discomfort, and leukorrhea.\textsuperscript{132,134} Histopathologic diagnosis is
available using CD138 staining to identify plasma cells within the endometrial tissue. However, the criteria for diagnosis of chronic endometritis are inconsistent. A systematic review and meta-analysis of 12 studies evaluating chronic endometritis in women affected by RPL reported an overall resolution rate of 87.9% after treatment. Treatment with antibiotic targeted antibiotic therapy varied from 8 to 21 days within the studies. Nonetheless, there are insufficient data to provide a solid recommendation for or against this evaluation and subsequent treatment.

**COUNSELING FOR COUPLES WITH RECURRENT PREGNANCY LOSS**

Discussing the likelihood of adverse outcomes in the event of pregnancy and in the long term is paramount in aiding couples with RPL in determining whether to continue pregnancy attempts. In this regard, Kolte et al developed an internally validated prognostic tool for patients with RPL to improve the prediction of successful live birth in subsequent pregnancies based on the individual’s age, comprehensive pregnancy history, and the number of previous pregnancy losses and live births and their chronologic sequence. Although it is yet to be externally validated, this tool has been recognized as helpful and endorsed by the ESHRE.

Regardless of the prognosis, pregnancy loss is a significant adverse life event, and the repetitive nature of RPL may exacerbate feelings of grief and guilt, putting patients with RPL and their families at risk for depression and anxiety. As such, health care professionals should acknowledge couples’ concerns, provide compassionate care, and offer referral for professional counseling when needed.

**CONCLUSION**

Recurrent pregnancy loss can cause significant distress for patients and their families. As described above, the pathophysiology of RPL can be multifactorial and the etiology often is not known, even after an extensive workup. We have grouped the potential causes of RPL into categories to guide evaluation. However, we realize that patients may have findings relevant to multiple categories that need optimization before another pregnancy attempt.

The evaluation for causes of RPL should encompass genetic, anatomic, endocrine, hematologic, environmental, and other potential etiologies. Patients with identified causes of RPL should be offered optimization and medical management within those therapies that have solid evidence to support their use. Recurrent pregnancy loss is unexplained in about half of cases. Unfortunately, there are insufficient data for many specific treatment options, especially for RPL of unknown etiology. Patients with RPL with no identified etiology should be reassured about the ultimately high successful live-birth rates should they continue to attempt conception. A holistic approach including supportive and empathetic care, psychological therapy resources, a plan for close-interval evaluation in the first trimester in subsequent pregnancies, and reassurance should be part of the standard care provided.

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