TOPICS IN OBSTETRICS & GYNECOLOGY

Clinical Obstetrics & Gynecology Continuing Education and Review

Update on Diagnosis and Management of Recurrent Early Pregnancy Loss

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Learning Objectives: After participating in this continuing professional development activity, the provider should be better able to:

1. *Define recurrent first-trimester pregnancy loss and list its causes.*
2. *Describe evaluation for recurrent first-trimester pregnancy loss.*
3. *Explain appropriate management for recurrent first-trimester pregnancy loss.*

Key Words: Recurrent miscarriage, Recurrent pregnancy loss

Recurrent pregnancy loss (RPL) is a disorder that poses many challenges to providers and patients. Clinically recognized pregnancy loss is estimated to occur in 15% to 25% of pregnancies, but the exact prevalence and incidence of RPL are unknown, because most countries do not have a nationwide registry.[1] Historically, RPL was defined as 3 or more pregnancy losses; however, since 2012, the American Society for Reproductive Medicine (ASRM) has redefined RPL to 2 or more clinical miscarriages.[1] Congruently, the European Society of Human Reproduction and Embryology (ESHRE) endorsed this updated definition in 2022.[2] ASRM, unlike ESHRE, excludes biochemical pregnancies from the definition of RPL; neither ASRM nor ESHRE includes ectopic and molar pregnancies in the definition.[1,2] RPL can be further divided into primary and secondary processes. Primary RPL refers to women who have never carried a pregnancy to viability (defined as 24 weeks' gestation), whereas secondary RPL includes those who experienced 2 or more clinical miscarriages after having had a previous live birth.[1] Regardless of whether the RPL is a primary or secondary process, it is vital to address the cause of this condition whenever possible and assess risk of recurrence.

Based on the previous definition of 3 or more pregnancy losses, the overall prevalence was presumed to be between 0.6% and 1.4%.[3] However, the number of women who meet criteria for RPL based on the current ASRM definition is substantially higher. According to a retrospective study of 2062 multiparous female physicians living in London, approximately 3.25% of women met criteria for RPL based the definition of 2 or more nonconsecutive miscarriages.[3] In the United States, it is estimated that less than 5% of

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women will experience 2 consecutive miscarriages; however, the exact prevalence is difficult to estimate.[1]

Interestingly, an increasing incidence of RPL may be informative about evolving changes in environmental or genetic risk factors predisposing women to pregnancy loss.[3] One retrospective nationwide registry-based study in Sweden demonstrated that the incidence of women with 3 or more consecutive pregnancy losses had increased by 74% from 2003 to 2012 among women 18 to 42 years old.[4] Investigators proposed the substantial increase in RPL may be attributed to a variety of causes, including increasing prevalence in risk factors, changes in environmental exposures, improvements in early pregnancy ultrasound, and a lower threshold for patients to seek care for RPL.[4] Additionally, more is being discovered regarding contributing lifestyle factors such as obesity, cigarette smoking, caffeine consumption, and illicit drug use.[1] Given its increasing incidence, RPL is a pressing clinical issue that physicians must be equipped to manage. This review summarizes recent updates and current recommendations for the evaluation and management of RPL.

Known Causes of RPL

Cytogenetic Abnormalities

Sporadic karyotypic abnormalities in products of conception (POC) are relatively common and can account for up to 60% of early pregnancy losses.[1] In one study, rates of cytogenetic abnormalities were compared between POC from women who underwent sporadic miscarriage and POC from women with RPL. Structural chromosomal abnormalities were detected at a higher rate in POC from women with RPL (12.1%) versus those with spontaneous miscarriage (6.6%), suggesting a genetic predisposition to nondisjunction and genomic instability in conceptions occurring in women with RPL.[5] Cytogenetic causes of RPL may occur due to chromosomal abnormalities resulting from a parental balanced rearrangement, which is independent of maternal age.[5] Nearly 2% to 5% of all couples with RPL have a parental structural chromosomal abnormality, which is higher than the 0.2% observed within the general population.[5]

Evaluation And Management of Cytogenetic Abnormalities

ASRM recommends peripheral karyotyping of all couples with RPL to detect balanced structural abnormalities.[1] Although not formally recommended by the ASRM or ESHRE, genetic evaluation of the POC can also be considered to aid in assessment of contributing causes.[2] Microarray-based comparative genomic hybridization (CGH) is the preferred method of POC analysis.[2] Unlike CGH, karyotype is limited by the risk of cell culture failure, and inability to distinguish maternal contaminant from a euploid female fetus.[6] Fluorescence in situ hybridization is also no longer in favor, as it is dependent upon probes for certain chromosomes and provides a limited view of the genome.[2] Microarray has become increasingly available and provides interpretable results in 91% to 99% of early pregnancy loss cases.[5] Results remain reliable even with maternal cell contamination rates from 3% to 22%.[6] One disadvantage of CGH is that the significance of copy number changes is not always known or clinically relevant.[6] Multiple newer techniques, including next-generation sequencing, whole-genome screening, and whole-exome screening, have emerged but are not well studied in POC evaluation.[2] Evaluating POC can help identify a genetic

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cause in 60% of cases.[1] However, regardless of whether a diagnosis is made based on this assessment, testing of the POC may be helpful psychologically for couples.[1] One study demonstrated that when performing a chromosomal microarray analysis of POC in addition to the recommended workup by ASRM, a probable cause is found in more than 90% of cases.[7] Therefore, combining a genetic evaluation of the POC with the above recommended workup may be a cost-effective approach that is highly successful in elucidating a cause for RPL.

Couples with parental structural chromosomal abnormalities may be offered in vitro fertilization (IVF) with preimplantation genetic testing to detect structural rearrangements (PGT-SR) and select unaffected embryos for transfer.[8] Ikuma et al[9] compared the live birth rate of 37 patients with RPL associated with a translocation undergoing PGT to 52 matched patients who chose natural conception. Although the cumulative live birth rates were similar (67.6% vs 65.4%, respectively), PGT-SR was found to significantly reduce the miscarriage rate from 58% in the natural conception group to 22% in the PGT group.[9] Although IVF with PGT-SR does not improve cumulative live birth rates in couples with RPL and a parental translocation, it may be offered as the reduction in miscarriage rate can provide psychological benefit. However, given insufficient data to support improvement in live birth rate, ASRM does not recommend its routine use.[1]

Structural Uterine Anomalies

Structural uterine anomalies associated with RPL include both congenital uterine anomalies and acquired pathologies. Congenital uterine anomalies are more commonly associated with second-trimester pregnancy loss and preterm labor, and their role in first-trimester RPL is controversial.[10] The prevalence of uterine anomalies is higher in those with a history of RPL (13.3%) compared with the general population (5.5%).[2] The most commonly identified anomalies in women with RPL included septate, bicornuate, and arcuate uteri.[11] A recent meta-analysis of 6 studies demonstrated that women with a septate [risk ratio (RR) 2.65, 95% confidence interval (CI) 1.39–5.09] or bicornuate uterus (RR 2.32, 95% CI 1.05–5.13) had an increased probability of first-trimester pregnancy loss compared with controls.[10] Although the pathogenesis of pregnancy loss in women with congenital uterine malformations is unclear, it may be attributed to reduced intrauterine volume, endometrial dysfunction, or poor vascular supply.[12] A septate uterus is associated with the poorest reproductive outcomes relative to other congenital anomalies, and accounts for 80% to 90% of all malformations among women with RPL.[13] The mechanism by which a septate uterus leads to pregnancy loss is unclear, but it has been postulated that poor vascular supply of the septum can lead to suboptimal implantation.[10]

The significance of acquired uterine malformations in RPL remains uncertain. There is no definitive evidence to support a role for uterine fibroids or endometrial polyps in RPL.[14] Studies in infertile women undergoing IVF suggest that implantation and pregnancy rates are negatively impacted by submucosal fibroids.[13] Mechanisms such as poor regional blood flow, abnormal vasculature, and inadequate decidual cell response are theorized to negatively impact pregnancy.[13] Additionally, adenomyosis has been implicated in pregnancy loss. A meta-analysis of 11 studies demonstrated lower clinical and ongoing pregnancy rates, and higher miscarriage rates among women with adenomyosis undergoing IVF treatment compared with those without.[15] Intrauterine adhesions are also associated with poor pregnancy outcomes; suspected mechanisms include destruction of the basal layer of the endometrium and adherence of the opposing uterine walls leading to compromise of the uterine cavity.[14] In a systematic review and meta-analysis reporting on 912 women, the pooled risk of intrauterine adhesions was higher in women with 3 or more prior miscarriages [odds ratio (OR) 2.1, 95% CI 1.09–4], but no significant increase in risk was seen in those with 2 versus 1 prior loss (OR 1.41, 95% CI 0.78–2.5).[14]

Appropriate Evaluation and Management of Structural Uterine Anomalies

Due to the higher prevalence of uterine malformations in women with RPL, diagnostic uterine imaging is indicated.[16] The initial evaluation of structural uterine abnormalities is often 2-dimensional (2D) transvaginal ultrasound because it is noninvasive and widely accessible; however, it is considered suboptimal due to its poor accuracy (low sensitivity, but high specificity) and limited ability to fully characterize malformations.[2,17] Three-dimensional (3D) ultrasound is preferred as it allows for visualization of the internal and external contours of the uterus and has a high sensitivity (83.3%–100% based on the anomaly being evaluated) and specificity (100%) for diagnosing uterine malformations.[18] Sonohysterography (SHG) provides more information than hysterosalpingogram (HSG) or ultrasound alone, and has a higher sensitivity (85%) and specificity (100%) than HSG or diagnostic hysteroscopy when diagnosing uterine malformations.[19] Pelvic MRI is only recommended when 3D ultrasound is not available.[8] Although MRI allows for assessment of the uterine cavity and fundus, with high sensitivity (92%) and specificity (100%), its practicality is still in question given the high cost and limited availability.[20]

When a uterine septum is detected, hysteroscopic septoplasty should be considered, as it is a low-morbidity intervention that can improve pregnancy outcomes, but there is a lack of robust evidence to support routine surgical management.[21] Pregnancy outcomes with a unicornuate uterus are also poor with approximately half of all recognized pregnancies resulting in failure during the second trimester.[13] Most unicornuate uteri are associated with a noncommunicating uterine horn, which should be removed if a functional cavity is present, to reduce risk for ectopic pregnancy and hematometra.[21] Additionally, 40% of unicornuate uteri are associated with ipsilateral renal agenesis, so further evaluation of the renal system is indicated.[2] With uterine didelphys or bicornuate uterus, unification procedures are unnecessary for most women.[21]

For acquired uterine anomalies such as adhesions (Asherman syndrome), submucosal fibroids, and polyps, hysteroscopic resection is recommended.[8] However, if uterine fibroids do not distort the uterine cavity and the patient is otherwise asymptomatic, then surgery is not indicated.[1] For intrauterine adhesions detected on SHG or HSG, hysteroscopy

is used for confirmation and operative management. Prognosis typically correlates to disease severity. Hysteroscopic adhesiolysis significantly decreases miscarriage rates from 40% to 80% to 7% to 23% post-correction.[13] As a last resort, a gestational carrier may be considered as an option for irreversible uterine anomalies.[8]

Immunologic Abnormalities: Antiphospholipid Syndrome

The immunologic etiology most relevant to RPL is antiphospholipid syndrome (APS), an acquired thrombophilia.[1] Approximately 5% to 20% of women will test positive for APS antibodies, which include 1) lupus anticoagulant, 2) anticardiolipin immunoglobulin G (IgG) or immunoglobulin M (IgM) antibody, and 3) anti-β2-glycoprotein IgG or IgM.[1] Although mechanisms underlying RPL are not definitive, antiphospholipid antibodies are thought to have an autoimmune effect leading to defective endovascular trophoblastic invasion rather than intervillous blood clots.[8,22] Antiphospholipid antibodies have been associated with decreased release of human chorionic gonadotropin from human placental explants leading to the prevention of in vitro trophoblast migration and invasion, and induction of an inflammatory response.[23]

Evaluation and Management of APS

The clinical diagnostic criteria for APS as defined by the antiphospholipid consensus group include 3 or more consecutive first-trimester losses before 10 weeks' gestation in the absence of other abnormalities.[24] However, ASRM and ESHRE support screening women for APS who have 2 or more early pregnancy losses when maternal anatomic and hormonal abnormalities and parental chromosomal abnormalities have been excluded.[22]

Diagnosis of APS is typically based on the Sapporo classification criteria: antiphospholipid antibodies must be present on 2 or more occasions 12 weeks apart.[22] The antiphospholipid consensus group established thresholds for these antibody levels, which include the following: 1) anticardiolipin antibody IgG or IgM in the serum or plasma present in medium or high-titer [>40 IgG phospholipid (GPL) or IgM phospholipid (MPL) units or >99th percentile] and 2) anti-β2-glycoprotein antibody IgG and/or IgM in the serum or plasma at a titer greater than the 99th percentile.[1] In addition to the laboratory criteria, clinical evidence of thrombosis or pregnancy morbidity must be present to establish the diagnosis of APS.[22] Pregnancy morbidity is defined as 1) one or more unexplained death at 10 weeks' gestation or more in a morphologically normal fetus, or 2) one or more preterm births of a morphologically normal neonate before 34 weeks' gestation, secondary to preeclampsia with severe features or eclampsia.[1] Once the diagnosis of APS is established, there is a proven benefit of treatment to improve outcomes in women with RPL. Treatment with unfractionated heparin in combination with a low-dose aspirin reduced early pregnancy loss by up to 50% in one systematic review of therapeutic trials.[25] However, there is no proven benefit to adding immunotherapy such as prednisone or IV immunoglobulin to low-dose aspirin when treating APS.[22]

Metabolic/Endocrine Abnormalities

Endocrine abnormalities such as uncontrolled maternal diabetes mellitus and thyroid dysfunction are both associated with RPL.[1,2] With respect to thyroid, multiple studies have shown an association between anti-thyroid peroxidase antibodies (anti-TPO), which are commonly associated with hypothyroidism, and RPL.[26] One meta-analysis demonstrated an increased risk of miscarriage in women with RPL who had anti-TPO antibodies, and the association persisted in euthyroid women who were positive for these antibodies.[26] Thus far there have been no high-quality studies demonstrating an association between overt hypothyroidism or subclinical hypothyroidism and RPL.[2,27] Currently, both ASRM and ESHRE endorse screening for thyroid dysfunction.[1,2] Although hyperthyroidism is associated with sporadic pregnancy loss and obstetrical complications, studies have not shown an association with RPL.[26]

Elevated prolactin levels may lead to ovulatory dysfunction associated with RPL through alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation.[1] No clear link has been established between hyperprolactinemia and RPL, but normalization of levels using a dopamine agonist can improve pregnancy outcomes in those with RPL.[1] Although some studies have reported an increased risk of miscarriage among patients with polycystic ovarian syndrome, its true impact on pregnancy loss is still controversial and routine testing is not recommended at this time.[8]

Evaluation and Management of Metabolic/Endocrine Abnormalities

ESHRE and ASRM recommend evaluation and treatment for diabetes mellitus and thyroid disorders in women with RPL.[8] Hemoglobin A_{1c} (HbA_{1c}) or a 2-hour 75-g oral glucose tolerance test (OGTT) is recommended to screen for diabetes mellitus; results of a 2-hour OGTT ≥200 mg/dL or an HbA1c ≥6.5% are consistent with the diagnosis of diabetes mellitus.[8] Because there is a direct correlation between HbA_{1c} levels and early miscarriage risk in women with diabetes mellitus, glucose control should be prioritized. Well-controlled diabetes mellitus is not a risk factor for RPL.[1]

A serum thyroid-stimulating hormone (TSH) level is the first-line test to evaluate for thyroid dysfunction, and if this is within normal range, routine testing of thyroxine (T4) levels or anti-thyroid antibodies is not recommended by ASRM.[1] Conversely, ESHRE does recommend screening for anti-TPO in women with RPL, even if euthyroid.[2,26] Among nonpregnant women, subclinical hypothyroidism is defined as a TSH greater than the upper limit of normal for a third-generation TSH assay (orsss >4.12 mIU/L in an iodine-sufficient area, if age-based upper limit not available) in the setting of a normal FT4.[27] The treatment of subclinical hypothyroidism remains controversial, but ASRM does not recommend treatment as it has not proven to reduce pregnancy loss or improve live birth rate.[27] It is widely agreed that overt hypothyroidism should be treated with levothyroxine.[8] Although data do not support a clear association between hyperthyroidism and RPL, hyperthyroidism should be treated to avoid perinatal complications.[8]

ASRM and ESHRE recommendations differ with respect to evaluation for hyperprolactinemia; whereas ASRM recommends measuring prolactin levels in women with RPL, ESHRE only recommends testing prolactin levels in women with RPL who have oligo/amenorrhea, which may be indicative of hyperprolactinemia.[2] Given that normalization of prolactin levels has been shown to improve pregnancy outcomes in patients with RPL, treatment of hyperprolactinemia with a dopamine agonist is recommended by both ASRM and ESHRE.[1,2,8]

Controversial Causes of RPL

Infectious Causes

Intrauterine infections leading to chronic endometritis have been associated with recurrent miscarriages, but the data remain controversial.[1] Pathogens including *Chlamydia trachomatis, Listeria monocytogenes, Ureaplasma urealyticum, Mycoplasma hominis*, rubella, cytomegalovirus, and herpes virus have all been identified in genital cultures from women with sporadic miscarriage.[1] However, given the lack of compelling data that these infections are associated with RPL, there is currently no recommendation to routinely screen for these infections.[1] If chronic endometritis is diagnosed on endometrial biopsy, treatment with antibiotics may be considered as a small observational cohort study demonstrated improvements in live birth rate from 74% to 88% in the treated group.[28]

Male Factors

Abnormalities in standard semen parameters are not correlated with RPL. Sperm DNA fragmentation has been investigated as a potential cause[1] but data remain contradictory on its association with RPL; therefore, ASRM does not recommend routinely screening for sperm DNA fragmentation during the evaluation of RPL.[6] Although there are several case-control studies that have shown an association between sperm aneuploidy and RPL, the clinical significance has not been validated.[6] Furthermore, testing of the POC in patients with RPL has not revealed an increased rate of sex chromosome aneuploidy.[1]

Inherited Thrombophilia

The hypercoagulable state of pregnancy is due to multiple factors including: 1) increased clotting factors (VII, VIII, X, von Willebrand factor, and fibrinogen); 2) decreased anticoagulant activity (protein S and acquired protein C deficiency); and 3) reduced fibrinolytic activity.[18] Mutations in the genes that either code for and/or regulate clotting factors can lead to inherited thrombophilias. The most common inherited thrombophilias include factor V Leiden, prothrombin deficiency, antithrombin deficiency, protein C deficiency, and protein S deficiency.[18] Women who are heterozygous for the 2 most common inherited thrombophilias, factor V Leiden and prothrombin mutations, are not at increased risk for RPL.[18] Therefore, the decision to screen a patient with RPL for thrombophilias should be based on both personal and family history. Women with inherited thrombophilias are at an even greater thrombotic risk during pregnancy, but there is no known association with recurrent early pregnancy loss. However, these patients should be evaluated and treated to improve pregnancy-related morbidity, including second-trimester losses, rather than for prevention of RPL.[18]

Alloimmune Factors

Studies investigating immunologic factors including human leukocyte antigen typing, embryotoxic factors, decidual cytokine profiles, and anti-paternal antibody levels

Table 1. Causes and Management of Recurrent Pregnancy Loss

Cause	Incidence	Recommended Evaluation	Management Options
Cytogenetic	2%–5%[1]	1. Offer parental karyotype to detect balanced chromosomal translocations[1] 2. Consider genetic evaluation of products of conception when available[2]	1. Offer preimplantation genetic testing for structural rearrangements (PGT-SR) if a balanced reciprocal translocation detected in either parent[6,9]
Structural uterine	1.8%–37.6% (mean 12.6%)[1]	1. Diagnostic uterine imaging[1,16] a. 3D transvaginal ultrasound (TVUS) preferred over 2D[17] b. Saline sonohysterography (SHG) preferred over hysterosalpingogram (HSG)[1,8] c. Pelvic MRI only if 3D TVUS not available[8] d. Hysteroscopy and laparoscopy are more invasive options[8]	1. Resection of septum[8] 2. Removal of noncommunicating uterine horn and ipsilateral fallopian tube if a functional cavity present[13] 3. Consider hysteroscopic correction of acquired uterine cavity abnormalities as clinically indicated (eg, submucosal myomas)[1,8]
Antiphospholipid syndrome	8%–42% (mean 15%)[1]	1. Testing for lupus anticoagulant, anticardiolipin antibody IgG and IgM, and anti-2-glycoprotein IgG and IgM on 2 separate occasions 12 weeks apart[1]	1. Treatment with heparin and low-dose aspirin[1,22]
Metabolic/ endocrine	Unknown	1. Screening for diabetes (hemoglobin A_{1c} or 2-hr glucose tolerance test)[1,8,26] and treatment 2. Screening for thyroid dysfunction with thyroid-stimulating hormone[1,8,26] 3. Obtain serum prolactin level[1,2,8,26]	1. Treatment of diabetes[1,2] 2. Correction of thyroid dysfunction[1,2] 3. Treatment of hyperprolactinemia[2]

have produced conflicting data.[1] Maternal immune tolerance is necessary for successful implantation and pregnancy, and thus, it is hypothesized that a disruption of the normal immune milieu of CD4 T-helper cells and uterine natural killer cells at the maternal-fetal interface could lead to implantation failure and pregnancy loss.[29] Aspirin, low-molecular weight heparin and the use of both in combination have been investigated; however, multiple randomized controlled trials have shown no benefit.[29] Corticosteroids and IV immunoglobulin have also produced conflicting data, and are not recommended by ASRM or ESHRE in the management of RPL (Table 1).[29]

Conclusion

RPL is an important reproductive health issue that requires more investigation. As per ASRM and ESHRE guidelines, evaluation and treatment can be initiated after 2 clinical pregnancy losses. Once a diagnosis of RPL has been made, screening for genetic factors, APS, assessment of uterine anatomy, and endocrinopathies is recommended.[1] In addition, although further investigation is needed to better elucidate the relationship between certain environmental exposures and RPL, it is reasonable to counsel all patients attempting conception on healthy lifestyle modifications. Women who experience RPL commonly report depression and anxiety, and although no causative link has been demonstrated, it is advisable to offer psychosocial support to patients or couples experiencing RPL.

Continued investigation is needed to optimize evaluation and treatment of patients with RPL, as up to 50% to 75% of cases have no causative factor identified, which can be frustrating for patients.[1] It is important that physicians provide proper counseling regarding prognosis. The prognosis of future pregnancies after a diagnosis of RPL is dependent on several factors, the largest contributors being number of losses and female age.[2] Although prognosis will clearly differ depending on cause and concurrent diagnoses, many women with RPL will ultimately achieve a live birth. The emergence of new data to more definitively identify causative factors for RPL will allow for improved diagnosis, prognostic counseling, and management of women suffering from this condition.

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1. How many pregnancy losses are required for the diagnosis of RPL, as defined by ASRM and ESHRE?
   - **A.** ≥1
   - **B.** ≥2
   - **C.** ≥3
   - **D.** ≥4

2. The preferred method of POC testing in cases of RPL is
   - **A.** karyotype.
   - **B.** fluorescence in situ hybridization.
   - **C.** microarray based-comparative genomic hybridization.
   - **D.** whole genome sequencing.

3. The uterine anomaly associated with the poorest prognosis in women with RPL is
   - **A.** uterine fibroids.
   - **B.** uterine polyps.
   - **C.** uterine septum.
   - **D.** bicornuate uterus.

4. Which one of the following is a recommended routine test for a patient with RPL?
   - **A.** sperm DNA fragmentation
   - **B.** sonohysterogram
   - **C.** screening for *Ureaplasma urealyticum*
   - **D.** endometrial biopsy

5. Patients with RPL and a structural uterine anomaly should be considered for
   - **A.** resection of uterine septum.
   - **B.** unification of bicornuate uterus.
   - **C.** removal of fibroids that do not distort the uterine cavity.
   - **D.** watchful waiting but not surgery in the event of a noncommunicating uterine horn that has a functional cavity.

6. Which one of the following is *not* considered an antiphospholipid antibody?
   - **A.** lupus anticoagulant
   - **B.** anticardiolipin antibody
   - **C.** antinuclear antibody
   - **D.** anti-2-glycoprotein

7. Treatment of RPL in women with APS includes
   - **A.** prednisone.
   - **B.** IV immunoglobulin.
   - **C.** aspirin.
   - **D.** low-molecular-weight heparin and aspirin.

8. Which one of the following screening tests for diabetes mellitus is recommended for women with RPL?
   - **A.** fasting blood glucose
   - **B.** 2-hour glucose tolerance test or hemoglobin A_{1c}
   - **C.** fasting insulin
   - **D.** none of the above

9. A 30-year-old woman with 3 consecutive pregnancy losses has a normal sonohysterogram and negative test for antiphospholipid antibodies. Additional laboratory testing should include
   - **A.** thyroid-stimulating hormone.
   - **B.** serum cytokine testing.
   - **C.** endometrial biopsy.
   - **D.** gonorrhea and chlamydia polymerase chain reaction.

10. All of the following are well-established causes of RPL, *except*
    - **A.** inherited thrombophilia.
    - **B.** antiphospholipid syndrome.
    - **C.** structural uterine anomalies.
    - **D.** cytogenetic abnormalities.

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