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Recurrent Pregnancy Loss in Obstetrics and Gynecology: An Evidence-Based Framework for Etiologic Evaluation, Risk Stratification, and Patient-Centered Management

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Abstract

Background: Recurrent pregnancy loss (RPL) is a complex and emotionally burdensome condition affecting approximately 2% of pregnant women. It is defined as two or more consecutive pregnancy losses in the U.S. and three or more in the U.K., with up to 50% of cases remaining unexplained despite comprehensive evaluation.

Aim: To provide an evidence-based framework for etiologic evaluation, risk stratification, and patient-centered management of RPL.

Methods: This review synthesizes current literature on RPL, including epidemiology, pathophysiology, diagnostic strategies, and management approaches. It emphasizes high-yield investigations such as endocrine screening, parental karyotyping, uterine imaging, antiphospholipid antibody testing, and genetic analysis of products of conception.

Results: RPL is multifactorial, involving genetic, anatomic, endocrine, immunologic, and lifestyle factors. Established interventions include endocrine optimization, surgical correction of uterine anomalies, and anticoagulation for antiphospholipid syndrome. Emerging therapies such as immunomodulators show limited evidence. Despite structured evaluation, many cases remain unexplained; however, prognosis is generally favorable with supportive care and multidisciplinary management.

Conclusion: Effective RPL care requires individualized, evidence-based evaluation, avoidance of low-value testing, and integration of psychosocial support. Multidisciplinary collaboration and patient education are essential to improve outcomes and reduce emotional distress.

Keywords:
Recurrent pregnancy loss, miscarriage, antiphospholipid syndrome, uterine anomalies, genetic counseling, evidence-based management.

Introduction

Recurrent pregnancy loss (RPL) represents a clinically significant and emotionally burdensome complication of reproduction, positioned at the intersection of obstetrics, gynecology, reproductive endocrinology, and psychosocial care. In the United States, RPL is commonly defined as two or more consecutive failed clinical pregnancies that have been documented by ultrasonography or confirmed by histopathology. [1] In contrast, clinical practice in the United Kingdom has historically applied a more stringent threshold, defining RPL as three or more consecutive early pregnancy losses. These definitional differences are not merely semantic; they influence the timing of evaluation, eligibility for specialized investigations, and the point at which clinicians initiate structured management pathways. Importantly, the trend toward earlier evaluation in

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some settings reflects recognition that repeated losses carry cumulative physical and psychological consequences and that earlier risk stratification may improve counseling and individualized care. Although miscarriage is relatively common as an isolated event, recurrent losses affect a smaller subset of patients. Epidemiologic estimates suggest that only approximately 2% of pregnant women experience two consecutive pregnancy losses, emphasizing that RPL is comparatively uncommon while still representing a substantial clinical workload within specialized services. [2] A defining feature of RPL is its etiologic heterogeneity. Potential contributors include chromosomal abnormalities, uterine structural pathology, endocrine and metabolic disorders, thrombophilias, and immune-mediated conditions; yet, despite comprehensive evaluation, a large proportion of cases remain unexplained. Indeed, up to 50% of patients with RPL do not have a clearly identified etiology. [3] This uncertainty complicates clinical decision-making and can intensify patient distress, as the absence of a definitive diagnosis may leave couples without an obvious therapeutic target and may foster anxiety regarding prognosis and the likelihood of future success.

RPL is widely regarded as one of the most complex scenarios in reproductive medicine because it demands both rigorous biomedical evaluation and sensitive, patient-centered communication. The experience of repeated pregnancy loss can generate profound grief, guilt, and anticipatory anxiety, and these psychosocial sequelae often persist into subsequent pregnancies. For clinicians, the challenge lies not only in identifying potentially modifiable risk factors but also in providing realistic counseling when the etiology is unclear, avoiding both therapeutic nihilism and unsupported interventions. Accordingly, modern RPL care increasingly emphasizes structured evaluation, evidence-based management, and multidisciplinary support, including mental health resources when appropriate. Clinically, RPL is often categorized as primary or secondary, distinctions that can be relevant for prognosis and etiologic considerations. Primary RPL refers to repeated pregnancy loss in individuals who have never achieved a live birth, whereas secondary RPL describes recurrent losses occurring after at least one prior live birth. [4] This classification acknowledges that reproductive history may reflect differing baseline risks and potentially distinct causal pathways, reinforcing the importance of individualized assessment and tailored counseling within obstetrics and gynecology practice [1][2][3][4].

Etiology

The etiology of recurrent pregnancy loss (RPL) is multifactorial and heterogeneous, reflecting the complex biologic requirements for normal implantation, placentation, and embryofetal development. In clinical practice, causation is often organized into broad domains—genetic, anatomic, endocrine/metabolic, antiphospholipid antibody syndrome, immunologic considerations, and environmental or lifestyle factors—recognizing that more than one contributor may coexist in the same patient. Even with comprehensive evaluation, a substantial proportion of cases remain unexplained, which reinforces the importance of evidence-based testing strategies and individualized risk assessment rather than indiscriminate investigation. Genetic factors, particularly fetal chromosomal abnormalities, are among the most common causes of miscarriage and play a major role in RPL. Aneuploidy—an abnormal number of chromosomes—frequently results from sporadic meiotic errors and can lead to early embryonic arrest or failed placental development. In addition to sporadic aneuploidy, parental chromosomal rearrangements may predispose to recurrent losses through the generation of unbalanced gametes. Balanced reciprocal translocations and Robertsonian translocations in one parent can be clinically silent in the carrier yet increase the risk of embryos with chromosomal imbalance, thereby elevating miscarriage risk. In this context, RPL may be the first clinical indicator of a parental karyotypic abnormality, and genetic counseling becomes essential to discuss prognosis and reproductive options. Anatomic causes encompass both congenital and acquired uterine abnormalities that interfere with implantation, uterine vascularity, or the capacity to sustain a growing pregnancy [5].

Congenital Müllerian tract anomalies are classically associated with pregnancy loss, particularly when they distort the uterine cavity or reduce functional endometrial surface area. Uterine configurations associated with RPL include septate, unicornuate, bicornuate, didelphic, and arcuate uteri. Among these, septate uterus is often cited as the most common congenital uterine anomaly and is particularly relevant because the septum may have suboptimal vascularization, potentially impairing implantation and placental development. A meta-analysis of multiple studies reported congenital uterine defects in approximately 12.6% of patients with RPL, supporting the clinical value of targeted anatomic evaluation in recurrent loss. [5] Acquired abnormalities can also contribute. Submucosal fibroids and endometrial polyps may disrupt the endometrial environment and mechanical support of implantation, while intrauterine adhesions (Asherman syndrome), often following uterine instrumentation or infection, can reduce endometrial receptivity and compromise placentation. Endocrine and metabolic contributors represent another important etiologic category because they are often modifiable. Maternal diabetes—particularly when poorly controlled—has been associated with increased miscarriage risk, likely through effects on early embryogenesis and placental function. Thyroid dysfunction similarly

warrants evaluation, as both overt hypothyroidism and hyperthyroidism can adversely affect pregnancy maintenance. Identification and appropriate treatment of these disorders is therefore a core component of RPL assessment. Hyperprolactinemia has been proposed as a contributor through disruption of gonadotropin-releasing hormone pulsatility and luteal function, but its causal relationship with RPL remains less firmly established, and clinicians must interpret prolactin abnormalities within the broader endocrine picture [5][6].

Antiphospholipid antibody syndrome (APLS) is the most clearly established acquired thrombophilia linked to RPL and is clinically significant because it has evidence-based treatment implications. Reported prevalence among patients with RPL varies widely—approximately 8% to 42%—reflecting differences in studied populations and diagnostic criteria. [6] APLS increases thrombotic risk and is associated with placental insufficiency, which can lead to early pregnancy loss and later obstetric complications. Because APLS is both diagnosable through validated laboratory criteria and treatable, its evaluation is a priority in the RPL workup. Environmental and lifestyle factors may also influence miscarriage risk through effects on trophoblastic function, vascular health, and endocrine-metabolic pathways. Cigarette smoking has been suggested to impair trophoblastic function and is associated with increased risk of pregnancy loss, making cessation counseling a relevant component of RPL care. Obesity is independently associated with higher RPL risk even among women who conceive naturally, and weight optimization may improve broader reproductive and metabolic health. Additional exposures linked to miscarriage risk include alcohol intake in the range of three to five drinks per week, cocaine use, and high caffeine consumption, commonly described as more than three cups of coffee per day. These associations support a preventive counseling approach that addresses modifiable behaviors while avoiding blame and acknowledging that many cases of RPL occur despite healthy lifestyles.

Finally, immunologic considerations are frequently discussed in RPL, but the evidence base does not support indiscriminate testing for inherited thrombophilias in all patients. Routine screening for hereditary thrombophilias is not currently recommended. [7] Instead, testing may be appropriate in selected patients, such as those with a personal history of venous thromboembolism occurring in the setting of a nonrecurrent risk factor (for example, surgery) or those with a first-degree relative with known or strongly suspected high-risk thrombophilia. Prospective cohort studies have not consistently confirmed a causal association between inherited thrombophilia and fetal loss, underscoring the need to reserve testing for scenarios where results would meaningfully alter management. In aggregate, the etiologic landscape of RPL demands careful, evidence-informed evaluation that prioritizes conditions with proven associations and actionable interventions while recognizing that multifactorial and unexplained cases remain common [7].

Epidemiology

Recurrent pregnancy loss (RPL) is an important clinical entity in obstetrics and gynecology, yet it affects a relatively small proportion of the pregnant population when compared with isolated, sporadic miscarriage. Epidemiologic estimates indicate that only about 2% of pregnant women experience two or more consecutive pregnancy losses, highlighting that RPL is uncommon while still representing a disproportionately high burden of clinical concern due to its emotional impact and the complexity of evaluation. [2] The relatively low population prevalence can also create practical challenges for research and guideline development, as large sample sizes are required to adequately study subgroups, uncommon etiologies, and the effectiveness of targeted interventions. A defining epidemiologic feature of RPL is the high frequency of unexplained cases. Even with contemporary diagnostic tools—including genetic evaluation, uterine cavity assessment, endocrine and metabolic screening, and testing for antiphospholipid antibody syndrome—a substantial proportion of patients do not receive a definitive etiologic diagnosis. Up to 50% of individuals with RPL have no clearly defined underlying cause, a statistic that is consistently cited across clinical literature and carries significant implications for counseling and management. [3] From a clinical standpoint, this means that many patients will undergo structured evaluation without identification of a singular, modifiable driver. From a public health and health-systems perspective, the high rate of unexplained RPL underscores the need for standardized, evidence-informed diagnostic pathways that avoid unnecessary testing and reduce exposure to unproven therapies while still ensuring that treatable conditions are not missed. The epidemiology of RPL also intersects with broader reproductive trends. As maternal age increases, the baseline risk of miscarriage rises, largely due to higher rates of fetal aneuploidy, which may indirectly increase the number of patients who meet criteria for recurrent loss. Additionally, the definition applied—two versus three consecutive losses—will influence reported prevalence and the timing of referral to specialty services. These considerations emphasize that epidemiologic estimates are not purely biologic measures; they also reflect how healthcare systems define RPL, how early losses are documented, and how consistently patients access evaluation and follow-up care. Ultimately, understanding RPL epidemiology requires balancing population-level rarity with the high individual-level impact and

recognizing that unexplained cases remain a major component of the clinical landscape [3][4].

Pathophysiology

Recurrent pregnancy loss (RPL) is best understood as a multifactorial disorder arising from disruption of the tightly coordinated processes required for successful conception, implantation, placentation, and early embryofetal development. In normal pregnancy, embryo implantation depends on endometrial receptivity, synchronized hormonal signaling, immune tolerance at the maternal–fetal interface, appropriate trophoblast invasion, and the establishment of a functional uteroplacental circulation. Failure at any point along this continuum—whether due to embryonic genetic abnormalities, uterine structural constraints, endocrine-metabolic dysregulation, prothrombotic or autoimmune mechanisms, or adverse environmental exposures—can culminate in pregnancy loss. Therefore, rather than representing a single disease entity, RPL frequently reflects converging biological vulnerabilities that differ between patients and may vary across successive pregnancies. From a genetic perspective, early loss is often driven by embryonic chromosomal errors that impair viability, while parental chromosomal rearrangements can increase the likelihood of recurrent unbalanced conceptions. These genetic abnormalities may impede early embryonic development, disrupt placental formation, or trigger implantation failure. Anatomical factors, particularly those that distort the uterine cavity or impair endometrial surface integrity, can compromise implantation stability and placental development through altered uterine perfusion, abnormal contractility, or reduced functional endometrial area. Endocrine contributors—including thyroid dysfunction, uncontrolled diabetes, or luteal-phase disturbances—can disrupt the hormonal milieu that maintains early pregnancy, influencing endometrial maturation, trophoblast invasion, and placental hormone production. In parallel, antiphospholipid antibody syndrome represents a well-established pathophysiologic mechanism for RPL by promoting thrombosis and placental insufficiency, thereby impairing oxygen and nutrient delivery during critical phases of pregnancy maintenance. Immunologic factors may also contribute through dysregulated maternal tolerance or abnormal inflammatory signaling at the maternal–fetal interface, while environmental exposures such as smoking, obesity-associated metabolic inflammation, alcohol, cocaine, and high caffeine intake may influence trophoblastic function, vascular health, and endocrine regulation. At the molecular level, emerging data increasingly implicate genes that regulate implantation biology and placental development in RPL susceptibility. FOXD1 mutations have been proposed as a central mechanistic contributor in some patients. FOXD1 has been characterized as a key molecule involved in embryo implantation in both mice and humans, in part through regulation of gene networks within the endometrium and placenta that support receptivity, trophoblast–decidual interaction, and early placental architecture. Functionally relevant FOXD1 mutations in humans have been linked to the origin of RPL, suggesting that altered transcriptional control of implantation-related pathways can create a permissive environment for implantation failure or early placental dysfunction, even in the absence of gross anatomic abnormalities or overt endocrine disease. [8] Clinically, this evolving pathophysiologic understanding reinforces that RPL should be approached through integrated evaluation rather than single-cause assumptions. It also underscores why many cases remain unexplained with traditional testing: molecular and regulatory defects in implantation and placentation may not be detected by routine karyotyping, imaging, or standard endocrine panels. As research clarifies how genetic regulators such as FOXD1 interact with immune, vascular, and hormonal pathways, future RPL management may increasingly incorporate refined risk stratification and targeted interventions aimed at the biology of endometrial receptivity and placental development rather than only structural or systemic factors [8].

History and Physical

A comprehensive history and physical examination form the cornerstone of recurrent pregnancy loss (RPL) evaluation because they establish the clinical phenotype, guide targeted investigations, and identify modifiable risk factors that may influence future outcomes. History-taking should be deliberate and structured, with careful documentation of every prior pregnancy and loss. For each event, clinicians should record gestational age at the time of loss, clinical presentation (e.g., bleeding, pain, preterm rupture of membranes), whether embryonic or fetal cardiac activity was documented, and whether loss was spontaneous or required intervention. The gestational age is particularly informative because RPL frequently demonstrates temporal clustering, meaning that losses often recur around a similar gestational window in successive pregnancies. This pattern can help narrow the differential diagnosis: very early losses may raise suspicion for embryonic chromosomal abnormalities or implantation failure, whereas later first-trimester or early second-trimester losses may increase concern for uterine cavity pathology, cervical insufficiency, antiphospholipid antibody syndrome, or placental dysfunction. Equally important is understanding the management of prior losses. The method of treatment—expectant management, medical management, or surgical uterine evacuation—can influence subsequent risk. Specifically, prior dilation and curettage may increase the likelihood of intrauterine adhesions (Asherman syndrome), which can compromise endometrial receptivity and placentation. In addition, cervical dilation procedures may contribute to cervical trauma and potential

cervical incompetence, a condition associated with pregnancy loss and preterm birth. Capturing these details allows clinicians to link prior interventions with plausible anatomic mechanisms and to determine whether uterine cavity assessment and cervical evaluation should be prioritized [8].

The broader medical history should include endocrine and metabolic conditions known to affect pregnancy maintenance, particularly thyroid dysfunction and diabetes, with attention to disease control, medication use, and recent laboratory values when available. Surgical history should be reviewed for prior uterine or cervical procedures, including myomectomy, hysteroscopic septum resection, cervical conization, or other interventions that may alter uterine anatomy or cervical integrity. Menstrual history is also relevant, as irregular cycles, intermenstrual bleeding, or dysmenorrhea may suggest endocrine disorders or uterine pathology such as polyps, fibroids, or chronic endometritis. A detailed obstetric and gynecologic history should further document fertility history, time to conception, use of assisted reproductive technologies, and any prior complications such as ectopic pregnancy or preterm birth. Because thrombotic and autoimmune mechanisms can contribute to RPL, clinicians should elicit both personal and family history of venous or arterial thrombosis, including age at onset, provoking factors, and any known thrombophilia diagnoses. Lifestyle and exposure history should be addressed explicitly, including smoking status, alcohol intake, illicit drug use, and potential exposure to environmental toxins, as these factors may influence trophoblastic function, placentation, and overall reproductive health. Medication and supplement histories should also be obtained, particularly anticoagulants, endocrine therapies, or immunomodulators. The physical examination should include a general assessment for signs of systemic disease, such as thyroid enlargement, features of poorly controlled diabetes, or clinical indicators of autoimmune disorders. A focused pelvic examination is essential to evaluate uterine size and contour, detect cervical or vaginal pathology, and identify signs suggestive of anatomic abnormalities. While the physical exam alone cannot diagnose many etiologies of RPL, it provides critical context, supports risk stratification, and ensures that subsequent testing is appropriately individualized rather than indiscriminate [8].

Evaluation

Evaluation of recurrent pregnancy loss (RPL) should be systematic, evidence-informed, and sufficiently comprehensive to identify treatable causes while avoiding tests with low clinical utility. Because RPL is etiologically heterogeneous, a structured approach is essential for accurate risk stratification and for providing realistic counseling regarding prognosis and management options. In contemporary obstetrics and gynecology practice, evaluation is typically organized into assessment of maternal medical conditions, genetic factors, uterine anatomy, and selected immunologic causes—particularly antiphospholipid antibody syndrome—along with judicious consideration of pregnancy tissue analysis when available. Assessment of underlying medical problems is a foundational step because endocrine and metabolic disorders can disrupt implantation, early placentation, and pregnancy maintenance, yet are often modifiable. Laboratory studies should be performed to evaluate for diabetes and thyroid dysfunction, as both uncontrolled glycemia and thyroid disease have been associated with pregnancy loss and may contribute to recurrent patterns if unrecognized. [9] Hyperprolactinemia is also commonly included in endocrine screening protocols, particularly when there are menstrual irregularities, galactorrhea, or other clinical features suggesting pituitary dysfunction. Identifying and treating endocrine abnormalities can improve overall reproductive health and may reduce recurrence risk in subsequent pregnancies. Genetic evaluation is another core component, reflecting the prominent role of chromosomal abnormalities in early pregnancy loss. Karyotype assessment of both partners should be offered to identify balanced reciprocal translocations, Robertsonian translocations, or mosaicism that may not affect the carrier's health but can generate unbalanced gametes and nonviable embryos, thereby predisposing to RPL. Although the diagnostic yield of parental karyotyping is relatively low and testing can be costly, it remains clinically relevant because confirmation of a rearrangement changes counseling, informs recurrence risk estimates, and may guide reproductive planning, including consideration of assisted reproductive technologies and genetic counseling. [10][11] The decision to pursue parental karyotypes should therefore be individualized, but the option should be discussed transparently with couples experiencing RPL.

Evaluation for uterine anomalies is essential because both congenital and acquired uterine pathology can compromise implantation or placentation and increase miscarriage risk. Multiple modalities are available, and selection depends on local resources, patient characteristics, and the clinical question. Pelvic ultrasound is frequently the initial test because it is noninvasive and can identify fibroids, endometrial polyps, and gross congenital anomalies. Saline infusion sonohysterography enhances visualization of the endometrial cavity and improves detection of intracavitary lesions and subtle contour abnormalities. Hysterosalpingography can provide information about uterine cavity shape and tubal patency, though it is less direct than sonohysterography or hysteroscopy for intracavitary detail. Diagnostic hysteroscopy remains the most

direct method for evaluating the uterine cavity and can be therapeutic when polyps, submucosal fibroids, adhesions, or septa are identified. Magnetic resonance imaging is particularly valuable for characterizing congenital uterine anomalies, especially when differentiating septate from bicornuate configurations, which can influence management decisions. [12] Because anatomic findings may be actionable—such as hysteroscopic septum resection or adhesiolysis—anatomic assessment is a high-yield aspect of the RPL workup. Immunologic evaluation should prioritize conditions with established associations and proven management implications. Antiphospholipid antibody syndrome (APS) is the most important acquired thrombophilia in this context, and testing is recommended for patients with RPL. Measurement of anticardiolipin antibodies, lupus anticoagulant, and anti–beta-2 glycoprotein I antibodies should be performed because studies have demonstrated associations between anticardiolipin antibodies and lupus anticoagulant with pregnancy loss. [13] Identifying APS is clinically significant because it provides a defined etiology and informs preventive strategies in future pregnancies.

In contrast, several historically used tests have limited utility and are not routinely recommended. Routine measurement of serum progesterone levels is not advised because it is not predictive of future pregnancy outcomes and does not reliably distinguish causal luteal-phase dysfunction from progesterone changes that are secondary to a failing pregnancy. Similarly, endometrial biopsy has not been shown to reliably reflect fertility status or provide actionable information for most patients with RPL, and large bodies of evidence have questioned its diagnostic value in this setting. Testing for infections in asymptomatic, otherwise healthy women is also low yield. Routine vaginal and cervical cultures for chlamydia, gonorrhea, bacterial vaginosis, or broad TORCH serologies do not meaningfully contribute to RPL evaluation in the absence of symptoms or specific clinical suspicion, and such testing can increase costs and anxiety without improving outcomes. A particularly valuable component of modern RPL evaluation is genetic analysis of products of conception (POC) when tissue is available from the second and subsequent losses. Using a 24-chromosome microarray analysis can substantially enhance diagnostic yield beyond traditional assessment pathways and adds meaningful information to the American Society for Reproductive Medicine (ASRM)–recommended evaluation. Offering genetic evaluation of miscarriage tissue obtained at the time of the second and subsequent pregnancy losses can help determine whether losses are attributable to sporadic aneuploidy versus other recurring maternal or uterine factors. When combined with an evidence-based clinical evaluation for RPL, POC genetic testing can identify a probable or definitive cause in more than 90% of miscarriages, thereby improving counseling and supporting more tailored management. [14] Overall, RPL evaluation is most effective when it integrates high-yield, actionable assessments with careful avoidance of low-value testing, ensuring that couples receive both rigorous medical investigation and clear, compassionate guidance [14].

Treatment / Management

Management of recurrent pregnancy loss (RPL) should be individualized and etiologically driven, with interventions targeted toward causes that are both demonstrably associated with loss and amenable to treatment. Because RPL affects not only reproductive outcomes but also psychological well-being, counseling and shared decision-making are integral components of care. Patients and their families should receive clear explanations regarding the risks, alternatives, and expected success rates of available interventions, with explicit acknowledgment of uncertainty when evidence is limited. Emotional support can improve engagement with evaluation and treatment, reduce anxiety in subsequent pregnancies, and strengthen adherence to follow-up plans. In practice, outcomes are optimized when care is coordinated through collaborative teamwork and clear communication among obstetricians, reproductive endocrinologists, maternal–fetal medicine specialists, genetic counselors, and—when needed—endocrinologists, hematologists, and mental health professionals [14].

Medical Conditions

Treatment of underlying medical disorders is a foundational strategy because many systemic conditions influence implantation, placentation, and early embryonic development. Women with thyroid disease, diabetes, obesity, and other relevant medical problems should be managed according to established medical standards, with the explicit goal of optimizing physiologic conditions before conception and throughout early pregnancy. Given the complexity of endocrine regulation in pregnancy, consultation with an endocrinologist is appropriate when thyroid disease or diabetes is uncontrolled or when medication adjustment is required preconceptionally or during early gestation. Particular attention is warranted in patients with elevated thyroid peroxidase antibodies, who are described as being at increased risk for RPL and therefore require careful endocrine assessment and appropriate management strategies. [15] In addition to thyroid and glycemic control, addressing obesity through sustainable weight optimization can improve metabolic and inflammatory profiles and may reduce overall reproductive risk, while also improving pregnancy health more broadly. Importantly, these interventions should be framed as supportive and health-promoting rather than punitive, recognizing that many individuals experience RPL despite meticulous attention to lifestyle.

Chromosomal Anomalies

When parental chromosomal abnormalities are identified, management begins with referral to genetic counseling. Genetic counseling serves several purposes: it clarifies the nature of the rearrangement, provides individualized recurrence risk estimates, and supports informed reproductive planning. Couples should be educated regarding the possibility of fetal chromosomal imbalance in future pregnancies and the range of available strategies to detect or mitigate this risk. Options may include prenatal genetic testing approaches such as chorionic villus sampling or amniocentesis, which can identify fetal chromosomal anomalies during pregnancy and support patient-centered decisions about ongoing management. Couples may also consider assisted reproductive approaches incorporating preimplantation genetic diagnosis or broader preimplantation genetic testing to identify genetic anomalies prior to embryo transfer. [16] However, it is also essential to counsel couples regarding the limitations of these approaches and the natural history of chromosomally unbalanced conceptions. Although embryos with unbalanced chromosomal arrangements can theoretically be screened out, preimplantation genetic testing (PGT) is not routinely advised in all cases of parental balanced rearrangements because the likelihood that a pregnancy with an unbalanced karyotype will survive into the second trimester is low [17]. This nuance matters clinically: it indicates that routine PGT may not always improve meaningful outcomes relative to its cost, complexity, and emotional burden, and the decision should be individualized based on age, reproductive history, fertility factors, and patient preferences. For some couples, the priority may be minimizing the chance of another loss even if most unbalanced conceptions would not progress; for others, the preferred pathway may be expectant management with early prenatal testing and supportive care.

Uterine Anomalies

Congenital and acquired uterine abnormalities represent a category in which surgical intervention may offer tangible benefit when a structural defect plausibly contributes to implantation failure or impaired placentation. Management should be based on careful anatomic characterization, ideally using imaging modalities that define the uterine cavity and external contour. When abnormalities are identified and judged clinically relevant, surgical correction can be considered. Procedures commonly discussed in RPL care include hysteroscopic septum resection for a septate uterus, hysteroscopic lysis of adhesions in Asherman syndrome, myomectomy for fibroids that distort the uterine cavity, and reconstructive procedures for selected congenital anomalies such as bicornuate uterus when indicated. Referral to a reproductive endocrinologist is appropriate for these interventions whenever feasible, as these specialists often have expertise in uterine cavity assessment, hysteroscopic techniques, and perioperative reproductive planning. [18] Surgical decision-making should remain individualized; not every anatomic variation requires correction, and the risks of surgery—including adhesion formation or uterine trauma—must be weighed against anticipated benefit.

Immunological Considerations

Among immunologic and thrombophilic factors, antiphospholipid antibody syndrome (APS) is the most clearly actionable condition. Patients with APS and RPL are generally treated with aspirin and heparin, and this strategy appears to improve pregnancy outcomes, likely by reducing thrombotic and placental insufficiency mechanisms. In contrast, in women with inherited thrombophilias, anticoagulation may improve certain maternal outcomes but does not reliably prevent RPL, highlighting the importance of distinguishing APS from other prothrombotic states and avoiding overgeneralization of treatment protocols. In many clinical settings, aspirin and low molecular weight heparin (LMWH) are commonly used medications in RPL care, yet only a limited number of placebo-controlled trials have demonstrated clear benefit specifically in terms of live birth rate, reinforcing the need for careful indication and transparent counseling. There is growing interest in novel immune-modulating therapies for selected RPL phenotypes. Emerging evidence suggests that agents such as tumor necrosis factor-alpha (TNF) inhibitors and granulocyte colony-stimulating factor (G-CSF) might be beneficial in certain cases, potentially by modifying inflammatory signaling or supporting implantation-related immune tolerance. However, the evidence base remains incomplete, and larger, well-designed clinical trials are required to confirm benefits, identify appropriate candidates, and clarify safety profiles in early pregnancy. [19] Lipid emulsion infusions have also been explored. In one randomized controlled trial, a 250 mL infusion administered on the day of oocyte retrieval—with additional infusions following a positive pregnancy test—was evaluated for the ability to increase chemical pregnancy rates in patients with RPL who had elevated peripheral blood natural killer (NK) cells (>12%) undergoing in vitro fertilization. The study concluded that intralipid supplementation did not increase chemical pregnancy frequency, though further investigation was suggested for outcomes such as ongoing pregnancy and live birth. [20] This finding illustrates a recurring theme in RPL therapeutics: biologically plausible interventions may not translate into improved clinically meaningful outcomes, and rigorous trials are essential before routine adoption.

Unexplained RPL

Unexplained RPL remains one of the most challenging scenarios because the absence of an identified etiology limits targeted intervention and increases patient anxiety. In this context, management is often centered on optimizing general health, providing early pregnancy surveillance, and avoiding unproven therapies that carry risk without demonstrated benefit. Evidence synthesis has raised important cautions about commonly proposed immunomodulatory treatments in unexplained cases. A recent meta-analysis applying strict criteria for defining unexplained recurrent miscarriage reported no randomized controlled trials evaluating prednisolone, indicating that evidence is insufficient to support routine use in this population. Additionally, two recent meta-analyses examining intravenous immunoglobulin (IVIG) in patients with RPL found no evidence of improved live birth rates, reinforcing that IVIG should not be routinely offered for unexplained RPL outside research settings. [21] Across all etiologic categories, effective RPL treatment depends on a transparent, supportive therapeutic relationship. Patients should be counseled that while certain causes—such as APS, uterine cavity pathology, and endocrine disorders—have more clearly established interventions, many cases remain unexplained and may still result in successful future pregnancies with supportive care and careful monitoring. Coordinated interprofessional management, combined with compassionate communication and evidence-based restraint in the use of low-value interventions, provides the best framework for improving both clinical outcomes and patient experience.

Differential Diagnosis

The differential diagnosis of recurrent pregnancy loss (RPL) should be approached as a structured hierarchy of common, high-prevalence mechanisms and less frequent but clinically actionable etiologies. Among the most common causes of repeated early losses are fetal chromosomal abnormalities, particularly sporadic aneuploidies arising from meiotic nondisjunction. These events are often age-related and account for a substantial proportion of first-trimester miscarriages. In the context of RPL, repeated aneuploid conceptions can occur by chance, especially with advancing maternal age, but they also raise consideration of parental chromosomal rearrangements and the value of evaluating products of conception to determine whether losses are genetically driven. Closely related to this is the category of idiopathic recurrent miscarriage, which remains common even after comprehensive evaluation. Idiopathic RPL is a diagnosis of exclusion and reflects both true biologic uncertainty and limitations of current diagnostic tools, including incomplete ability to detect subtle implantation, placentation, or immunologic abnormalities. Uncommon but high-impact differentials include antiphospholipid syndrome (APS), cervical incompetence, parental chromosomal abnormalities, and endocrine disease such as uncontrolled diabetes. APS is especially important because it is one of the few immunologic conditions with a well-established association with pregnancy loss and with evidence-based management strategies. Cervical incompetence is typically associated with later losses or early preterm birth and should be considered when the clinical narrative involves painless cervical dilation, membrane prolapse, or recurrent second-trimester losses at similar gestational ages. Parental chromosomal abnormalities—such as balanced reciprocal or Robertsonian translocations—may be clinically silent in carriers but predispose to embryos with unbalanced karyotypes, leading to recurrent miscarriage. Although the yield is relatively low, identification changes counseling and can guide reproductive planning and testing strategies. Uncontrolled diabetes is another less common but clearly modifiable contributor; hyperglycemia can impair early embryogenesis and placentation, and it warrants careful assessment and optimization before conception and in early pregnancy. Importantly, these causes are not mutually exclusive. A patient with idiopathic RPL may still have modifiable risk factors, and a patient with a uterine or cervical issue may also experience sporadic aneuploidy-related losses. Therefore, a robust differential diagnosis is best built by integrating the gestational timing pattern of losses, prior ultrasound and pathology data, interpregnancy history, endocrine and thrombotic risk profiles, and—when available—genetic evaluation of miscarriage tissue. This integrated approach supports targeted testing, avoids low-value investigations, and enables patient-centered counseling that aligns etiologic probability with clinical actionability [20][21].

Pertinent Studies and Ongoing Trials

Clinical trials addressing RPL have increasingly focused on therapies that are biologically plausible, widely accessible, and potentially capable of supporting early pregnancy maintenance in otherwise unexplained cases. Progesterone supplementation has been a central theme within this research agenda because progesterone is critical for endometrial receptivity, immunologic tolerance at the maternal–fetal interface, and maintenance of early gestation. The Progesterone in Recurrent Miscarriage (PROMISE) trial is among the most influential randomized controlled trials in this area. It enrolled 836 women with idiopathic recurrent miscarriage and randomized participants to receive either 400 mg of vaginal micronized progesterone twice daily or placebo, initiated at the time of a positive pregnancy test and continued through 12 weeks of gestation. The trial reported no significant difference between the progesterone and placebo groups in miscarriage rates or live birth rates, suggesting that progesterone initiated after pregnancy confirmation may not

improve outcomes for idiopathic RPL as defined in that study. [22] In contrast, another randomized controlled trial involving 700 women evaluated a similar progesterone dose and route but employed a different timing strategy. Rather than beginning treatment after a positive pregnancy test, the intervention commenced in the luteal phase immediately after ovulation confirmation, using ultrasound or luteinizing hormone (LH) kits, and continued until 28 weeks gestation. This Egyptian study reported significantly lower miscarriage rates (12.4% versus 23.3%) and higher live birth rates (92% versus 77%) in the treatment arm. [23] The contrast between these two trials is clinically instructive because it highlights how timing, patient selection, and protocol design may influence treatment effects. Initiating progesterone earlier may better support implantation and early placentation, whereas later initiation may miss a critical biologic window in some patients. However, differences in population characteristics, baseline risk profiles, and healthcare contexts also likely contribute, and these discrepancies reinforce the need for cautious interpretation and further high-quality trials that harmonize definitions, stratify by phenotype, and measure clinically meaningful endpoints. Ongoing research continues to refine which subgroups may benefit from progesterone—such as women with early pregnancy bleeding or those with specific luteal or endometrial profiles—and to explore alternative adjuncts aimed at implantation biology and placental development. As the field evolves, the central methodological challenge remains distinguishing interventions that improve live birth rates from those that primarily modify intermediate outcomes, and ensuring that therapies are adopted only when benefits clearly outweigh costs and potential harms [22].

Prognosis

The prognosis of recurrent pregnancy loss must be framed in both medical and psychosocial dimensions. Clinically, many couples ultimately achieve a live birth, including a substantial proportion of those with unexplained RPL, yet the pathway is often prolonged and emotionally taxing. RPL exerts a profound psychological impact and is strongly associated with grief, depression, anxiety, and diminished self-esteem, particularly when losses are repeated and the etiology is uncertain. This emotional burden often intensifies in subsequent pregnancies, where the anticipation of miscarriage can dominate the early gestational experience and complicate bonding, sleep, and daily functioning. Prognostic counseling therefore requires sensitivity and clarity, acknowledging both the distressing history and the realistic possibility of future success. From an obstetric perspective, the most influential independent predictors of subsequent pregnancy loss are increasing maternal age and the number of prior miscarriages. These factors likely reflect both biologic and probabilistic dynamics. Maternal age correlates with increasing rates of embryonic aneuploidy, which raises miscarriage risk regardless of other conditions. The number of prior losses also serves as a marker of baseline vulnerability—whether due to unrecognized biologic factors, persistent anatomic or endocrine contributors, or chance recurrence of sporadic chromosomal events. Although these predictors are useful in broad risk stratification, they cannot fully determine an individual couple's outcome, particularly when a treatable cause is identified and effectively managed. A key feature of prognosis is the tension between uncertainty and hope. Even when investigations reveal no definitive cause, many couples will still have a high likelihood of live birth over time. Accordingly, prognostic discussions should avoid therapeutic nihilism and should emphasize what can be optimized—general health, management of endocrine disease, correction of uterine cavity pathology when indicated, and evidence-based treatment for antiphospholipid syndrome—while maintaining realistic expectations about what medicine can and cannot guarantee. In well-structured care pathways, prognosis improves not only through targeted interventions but also through consistent follow-up, early pregnancy monitoring when appropriate, and psychological support that helps couples navigate repeated uncertainty [22].

Complications

Complications of recurrent pregnancy loss extend beyond physical outcomes and are predominantly psychosocial, relational, and behavioral, although medical consequences can also occur through repeated procedures or pregnancy complications in subsequent gestations. Emotionally, women and couples may experience prolonged grief, persistent anxiety, depressive symptoms, and intrusive fears about future pregnancies. The cyclical pattern of hope followed by loss can create a sense of helplessness and a belief that the problem may never resolve, which may contribute to social withdrawal, impaired occupational functioning, and reduced quality of life. Many couples describe an ongoing state of vigilance and apprehension, where each new pregnancy is simultaneously desired and feared, resulting in a chronic psychological burden. RPL can also strain relationships. Repeated loss may generate anger, sadness, frustration, and confusion, and partners may grieve differently, leading to misalignment in coping strategies and communication. Over time, this can affect intimacy, contribute to sexual difficulties, and create tension around timing of conception attempts, medical appointments, and financial expenditures on evaluation or treatment. The impact may be compounded by external pressures, including family expectations, cultural stigma, and feelings of

isolation when others minimize early pregnancy loss or do not recognize its severity. Medical complications may arise indirectly. Recurrent dilation and curettage can increase the risk of intrauterine adhesions, which may affect future fertility and pregnancy outcomes. Repeated pregnancies and losses may also increase anemia risk, contribute to pelvic infection risk in the setting of procedures, and create cumulative exposure to medications or interventions of uncertain benefit. In addition, the stress associated with RPL can influence health behaviors, including disrupted sleep, poor nutrition, increased substance use, or avoidance of healthcare. Clinicians are also affected; repeated unsuccessful outcomes can contribute to professional frustration and moral distress, particularly when evidence-based options are limited. Recognizing these complications reinforces that RPL care should include psychological assessment, supportive counseling, and referral pathways, rather than focusing exclusively on biomedical testing [19][18][20].

Consultations

Optimal management of recurrent pregnancy loss frequently requires multidisciplinary consultation because etiologies span genetics, endocrinology, uterine anatomy, thrombosis, immune conditions, fertility care, and mental health. An obstetrician–gynecologist with specific expertise in RPL is often the coordinating clinician, integrating investigations, counseling, and pregnancy planning. Reproductive endocrinology and IVF specialists may be involved when advanced fertility treatment is needed, when genetic testing strategies are considered, or when surgical management of uterine anomalies is best provided through fertility-focused services. An infertility-specialized nurse can contribute significantly through patient education, continuity of care, coordination of appointments, and support during emotionally intense decision-making. Genetic consultation is essential when parental karyotype abnormalities are identified or when pregnancy tissue analysis suggests chromosomal mechanisms, as geneticists and genetic counselors provide recurrence risk interpretation and options for prenatal or preimplantation testing. Mental health specialists, psychotherapists, and bereavement counselors play a critical role in addressing grief, anxiety, and depressive symptoms, and in supporting coping strategies and relationship stability. When antiphospholipid syndrome or complex thrombotic histories are present, hematologists are valuable for interpreting antibody profiles, assessing thrombosis risk, and guiding anticoagulation strategies in pregnancy. Immunologists may be involved in complex or research-oriented cases where immune dysregulation is suspected and where investigational therapies are being considered. Endocrinologists are appropriate when diabetes or thyroid disease is uncontrolled, when autoimmune thyroid patterns complicate management, or when broader endocrine disorders such as hyperprolactinemia require specialist input. A consultation framework should be individualized, emphasizing that multidisciplinary involvement is not a reflection of poor prognosis but rather a strategy to ensure that treatable contributors are addressed comprehensively and that patients receive coordinated, coherent guidance rather than fragmented care [20][23].

Patient Education

Patient education is fundamental to the successful management of couples with recurrent pregnancy loss because it shapes expectations, improves engagement with evaluation, supports adherence to recommended interventions, and reduces the psychological harm associated with uncertainty. Effective education begins with a sensitive clinical approach that recognizes RPL as a major life event, validates grief, and avoids language that implies blame. Clinicians should actively explore the couple's concerns, preferences, and goals, while also acknowledging cultural differences, religious considerations, and personal values that influence decisions about testing, interventions, and pregnancy continuation. When patients feel heard and respected, they are more likely to participate meaningfully in shared decision-making and to maintain follow-up in what is often a prolonged clinical pathway. Education should clarify the definition of RPL, the purpose of evaluation, and the distinction between treatable causes and unexplained cases. Couples benefit from understanding that many investigations are designed to identify conditions with evidence-based interventions—such as antiphospholipid syndrome, uterine cavity abnormalities, or endocrine dysfunction—while also recognizing that testing may not yield a definitive diagnosis. Written information leaflets and reliable resources can improve comprehension and reduce reliance on misinformation, particularly in online environments where unproven therapies are frequently promoted. Preconception counseling should address modifiable risk factors, including smoking, alcohol intake, and high caffeine consumption, and should encourage folic acid supplementation in preparation for pregnancy. Education should also include guidance on when to seek early pregnancy care, how surveillance may be structured in future pregnancies, and what symptoms warrant urgent evaluation. Deterrence in this context refers to reducing avoidable harm—especially the harms of unproven interventions, fragmented care, and untreated mental health needs. Patients should be counseled that no single recommendation guarantees pregnancy success, and that over-medicalization can sometimes increase stress without improving outcomes. At the same time, couples should be reassured that many individuals with RPL ultimately achieve a live birth, often even without specific treatments, which can protect hope while maintaining realism. Screening for anxiety and depression and prompt referral when

needed should be framed as routine aspects of RPL care, not as secondary considerations. Ultimately, education functions as a therapeutic intervention: it improves coping, supports rational decision-making, and enhances the likelihood that couples will navigate future pregnancies with structured support rather than fear-driven uncertainty [21][22][23].

Enhancing Healthcare Team Outcomes

Improving outcomes in recurrent pregnancy loss requires interprofessional collaboration that is both clinically coordinated and emotionally attuned. RPL is complex and often frustrating for patients and clinicians because investigations can be extensive, results may be inconclusive, and evidence-based treatments are limited in unexplained cases. Therefore, thorough counseling is essential so that patients can decide whether they wish to pursue comprehensive evaluation and which interventions align with their values and tolerance for uncertainty. Collaboration among obstetricians, reproductive endocrinologists, geneticists, endocrinologists, nurses, and midwives allows care to be both comprehensive and coherent, minimizing contradictory messages and reducing delays in addressing treatable conditions. Nursing care is central to effective RPL pathways. Nurses assist clinicians by coordinating investigations, ensuring that testing is completed efficiently, and providing education about possible etiologies and the rationale for each component of evaluation. Because counseling in RPL requires sensitivity, nursing support helps sustain patient engagement, particularly when results are uncertain or when couples face repeated disappointments. Providing written information materials supports informed decision-making and reduces anxiety associated with complex terminology. Ideally, patients are counseled preconceptionally about modifiable risk factors such as smoking, alcohol use, and caffeine intake, and are advised regarding folic acid supplementation. In subsequent pregnancies, regular follow-up visits can provide reassurance, enable early identification of complications, and create a structured environment for monitoring. Mental health integration further enhances outcomes. Nurses and clinicians should actively screen for depression and anxiety, recognizing that psychological distress is common and can worsen with repeated losses. Rapid referral to mental health professionals should be available when indicated, and psychotherapy may be beneficial for coping, grief processing, and relationship support. Equally important is honest prognostic counseling: couples should be informed that no intervention guarantees success, yet they often retain a high chance of achieving a live birth even after multiple losses. This balanced message can reduce catastrophic thinking while supporting realistic planning. Finally, the healthcare team should ensure access to community resources, including patient support groups, bereavement services, and culturally appropriate counseling. Support groups can reduce isolation and provide peer validation, which is particularly important when couples feel misunderstood by family or society. Harmonious collaboration—grounded in patient-centered care—links biomedical evaluation with psychosocial support and improves both the likelihood of a successful pregnancy and the overall well-being of couples navigating recurrent loss [19][20][21][22][23].

Conclusion:

Recurrent pregnancy loss represents one of the most challenging conditions in reproductive medicine due to its multifactorial etiology and profound psychological impact. While identifiable causes such as endocrine disorders, uterine anomalies, and antiphospholipid syndrome allow targeted interventions, nearly half of cases remain unexplained, underscoring the need for structured, evidence-informed evaluation rather than indiscriminate testing. Management should prioritize treatable conditions, optimize general health, and incorporate early pregnancy surveillance, while avoiding unproven therapies that increase cost and anxiety without improving outcomes. Equally critical is addressing the emotional burden of RPL. Repeated losses often lead to grief, anxiety, and relationship strain, making mental health support and patient education integral to care. Prognosis remains optimistic for many couples, even in unexplained cases, provided care pathways emphasize realistic counseling, multidisciplinary collaboration, and compassionate communication. Future research should focus on refining risk stratification and exploring molecular mechanisms of implantation and placentation to develop targeted therapies. Ultimately, successful RPL management combines biomedical rigor with psychosocial sensitivity, ensuring that patients receive comprehensive, coherent, and empathetic care throughout their reproductive journey.

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