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A Comprehensive Review Of Recurrent Pregnancy Loss Etiologies

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Abstract: Recurrent pregnancy loss (RPL) is a major reproductive health concern worldwide. It affects around 2%-3% of women of reproductive age and can seriously harm their physical and mental health. The cause remains unknown in about half of all cases, creating a significant challenge for clinical care. RPL is widely viewed as a complex condition with many possible causes. Identified risk factors include maternal age, genetic factors, structural abnormalities, endocrine disorders , a prethrombotic state, immune factors and infection. Advances in next-generation sequencing have greatly improved the ability to detect chromosomal changes and single-gene variants linked to RPL. These findings offer new insight into how the condition develops. Specific treatment advice has also been developed based on diagnostic assessments and the identified cause. This review summarizes current knowledge and recent advances in RPL, with particular attention to immune and genetic causes, clinical diagnosis and treatment.

Keywords: etiological diagnosis; genetic causes; next-generation sequencing; recurrent pregnancy loss; treatment recommendations

I. Introduction

The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) define recurrent pregnancy loss (RPL) as two or more spontaneous pregnancy losses before 20 weeks of gestation [1]. The latest Chinese expert consensus defines RPL as two or more consecutive losses with the same partner before 28 weeks of gestation [2]. ESHRE recommends using "recurrent pregnancy loss" as a general term for repeated losses, and "recurrent miscarriage" for repeated miscarriages within the uterus [3]. RPL covers losses after natural conception and assisted reproductive treatment (ART). It does not include ectopic or molar pregnancies, or implantation failure [4]. Whether the definition should include non-consecutive or biochemical losses remains disputed among countries and international societies.

Estimating the prevalence of RPL is difficult. Rates vary with the patient groups studied and the definitions and guidelines used. One report found that recurrent miscarriage (RM) affects around 0.8%-1.4% of women when only repeated intrauterine losses confirmed by ultrasound or histopathology are counted. When losses that are not seen on scans, such as biochemical pregnancies, are included, the rate rises to 2%-3% [5].

RPL is a major reproductive health concern worldwide and one of the most challenging issues in reproductive medicine. More than 50% of couples with RPL have no clear explanation for their losses [6]. Unlike a single pregnancy loss, RPL often calls for further medical care and close monitoring in later pregnancies. It is widely accepted as a multifactorial condition. Possible causes include chromosomal aneuploidy, uterine defects, immune dysfunction, endocrine disorders, genetic variants and lifestyle factors

[7]. In unexplained RPL (URPL), none of these factors is found to explain the losses. This makes diagnosis and treatment difficult for clinicians and causes severe psychological distress for couples.

This review examines current knowledge of RPL diagnosis, causes and management. It also discusses new findings on the immune and genetic causes of RPL. Epidemiology of RPL Earlier epidemiological studies indicate that RPL rates have risen each year worldwide [1]. Advanced maternal age is a major risk factor. Many studies show that miscarriage risk is lowest among women aged 20-29, rises sharply after 30 and can exceed 50% after age 45 [8].RPL has several distinct features. First, its risk is linked directly to previous pregnancy outcomes [9], [10], [11], [12]. Women who have had one miscarriage are less likely to have another. Each further miscarriage raises the risk of RM by 10%. The risk can exceed 40% among women with three or more losses [8]. Second, clinically identified RPL occurs in about 1% of women, above the expected rate of 0.34% [13]. Third, couples with RPL have fewer fetal chromosomal abnormalities than those with a single spontaneous miscarriage [14]. Fourth, RPL is more common among women with certain reproductive histories, including intrauterine growth restriction (IUGR), late miscarriage, stillbirth, neonatal death, ectopic pregnancy or preterm birth [15], [16], [17], [18].

Some cases of RPL may be linked to harmful environmental conditions, psychological factors and unhealthy habits [19]. Potential environmental risks include air and water pollution, radiation, unsuitable temperatures and poor nutrition [20]. Distress, hostility and anxiety during pregnancy have also been strongly associated with RPL [2, 21, 22]. In addition, many national and international guidelines and consensus statements link adverse lifestyle habits and psychological factors with RPL [3, 19]. They advise patients with RPL to stop smoking, avoid excessive alcohol consumption, maintain a healthy body mass index (BMI) and seek psychological support when needed.

1. Primary risk factors for RPL

The causes of RPL are complex. Several main risk factors have been identified, including genetic factors, anatomical abnormalities, endocrine disorders, prethrombotic states, immune imbalance and infection. Genetic factors and maternal immune dysregulation are considered two of the most important causes and are discussed in detail below.

Anatomical factors account for about 16% of RPL cases, a higher rate than that of uterine abnormalities in the general female population [20, 21]. These include congenital uterine anomalies, such as septate, arcuate, bicornuate, unicornuate and double uterus, as well as acquired abnormalities, including intrauterine adhesions (IUA), uterine fibroids and adenomyosis. Endocrine disorders also increase the risk of RPL. These include abnormal thyroid function, hyperprolactinemia (HPRL), luteal phase deficiency (LPD) and polycystic ovary syndrome (PCOS). They are found in around 8%–12% of patients with RPL [22]. Endocrine-related pregnancy loss often occurs early in pregnancy. This suggests that hormonal regulation is important for embryo attachment and early implantation in the uterus [23].

A degree of maternal blood hypercoagulability is a normal change during pregnancy [24]. Excessive hypercoagulability, however, can cause a pathological prethrombotic state (PTS), which raises the risk of clot formation. Studies have linked both hereditary and acquired PTS with a higher risk of RPL [25, 26]. Hereditary PTS results from mutations in genes involved in anticoagulation, coagulation or fibrinolysis. Acquired PTS includes antiphospholipid syndrome (APS), acquired hyperhomocysteinemia (HHcy) and other thrombotic disorders. In the Han population, PTS caused by factor V Leiden (FVL) or coagulation factor II mutations is rare, while protein C and protein S deficiencies are more common. The pattern is reversed in European and American populations.

Bacterial and viral infections may also raise the risk of RPL. Studies have reported links between bacterial vaginosis, reproductive tract dysbiosis and RPL, but their findings are inconsistent [27, 28]. Chronic endometritis, which may result from infection, is more common among patients with infertility, recurrent implantation failure (RIF) and RPL. Oral antibiotic treatment may improve pregnancy outcomes in this group [29]. Further randomized controlled trials (RCTs) are needed to confirm the link between infection and reproductive failure and provide more reliable evidence.

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2. Immunological factors in the etiology of RPL

2.1 Maternal immune dysregulation is associated with RPL

Maternal immune dysregulation is considered one of the leading causes of RPL [30]. Patients with a history of RPL often have autoimmune abnormalities or alloimmune problems [31]. Autoimmune abnormalities may contribute to RPL through the production of tissue-specific or non-tissue-specific autoantibodies. Non-tissue-specific antibodies include antiphospholipid antibodies (aPLs) and antinuclear antibodies (ANAs). Tissue-specific antibodies include anti-sperm and anti-ovarian antibodies. These autoantibodies may attack the mother's tissues and placenta, damage vascular endothelial cells and lead to pregnancy loss.

Alloimmune problems can also cause RPL by disrupting immune tolerance at the maternal-fetal interface. Immune factors have become a major focus of research into RPL. However, the immune cells and factors involved in these responses are complex, and research remains at an early stage. Further detailed studies are needed.

2.2 Autoimmune diseases and RPL

Autoimmune diseases (AID) are chronic inflammatory conditions in which the immune system responds to self-antigens and damages the body's own tissues. Studies have linked APS [32], systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), rheumatoid arthritis (RA), systemic sclerosis (SSc) and undifferentiated connective tissue disease (UCTD) with a higher risk of RPL. Women with SLE have a spontaneous miscarriage rate of about 20%, particularly in the middle and later stages of pregnancy. Their stillbirth rate is two to four times that of women with uncomplicated pregnancies.

Common autoantibodies, including aPLs and ANAs, have been found in patients with these co-existing AID and are also linked to RPL. aPLs are sensitive indicators of fetal distress or death and are found in almost all stillborn patients with SLE. The main types are lupus anticoagulant (LA), anticardiolipin antibody (aCL) and anti-β2 glycoprotein I antibody (aβ2GPI) [33]. Non-classical aPLs have also been linked to RPL. These include anti-β2GPI domain I antibody, anti-prothrombin antibody (aPT-A) and anti-phosphatidylserine/prothrombin complex antibody (aPS/PT) [34].

ANAs are autoantibodies that bind to DNA, RNA, proteins or molecular complexes in the cell nucleus. More than 20 types have been identified. Studies show that repeated pregnancy loss is often linked to a higher rate of ANA positivity. Among patients with RPL, reported ANA positivity ranges from 8% to 50%. It is 38.1% in patients with two consecutive miscarriages and rises to 43.5% in those with three or more consecutive miscarriages.

2.3 antiphospholipid syndrome and RPL

APS is an AID characterized by recurrent arterial or venous thrombosis, RPL, thrombocytopenia and persistently positive serum aPLs. Obstetric APS (OAPS) refers to APS with pregnancy complications as its main clinical feature [35]. Non-criteria OAPS (NOAPS) describes cases with typical clinical features or typical laboratory findings alone.

The main target antigens of aPLs are β2GPI and prothrombin. These antibodies play a key role in APS-related RPL. Under pathological conditions, more open-form β2GPI accumulates on decidual endothelial cells, villi and extra villous trophoblasts. This form binds readily to aPLs. The resulting aPL-β2GPI complexes can activate the complement system and affect coagulation, increasing fibrin deposits and placental vascular thrombosis. They can also disrupt angiogenesis and spiral artery remodeling, inhibit trophoblast cell growth and differentiation, and trigger apoptosis by promoting inflammation. Patients with RPL caused by OAPS need careful attention. Non-standard aPL tests may be useful when classical aPL tests are negative despite clear clinical symptoms.

2.4 Alloimmune risk factors in RPL

Early studies linked alloimmune-related RPL to an imbalance between Th1 and Th2 cells. More recent research has associated an imbalance between Tregs and Th17 cells with a higher risk of unexplained RPL (URPL). Tregs suppress inflammation and have strong immunosuppressive effects, whereas Th17 cells promote inflammatory responses [36]. Interleukin-17 (IL-17), produced by Th17 cells, has a key role in acute inflammation and autoimmune responses. It is also a major immunological risk factor for RPL.

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Studies show that RPL may be linked to increased numbers or activity of Th17 cells, or to reduced numbers or impaired function of Tregs. Abnormal numbers and activity of natural killer (NK) cells have also been linked to RPL. Decidual NK (dNK) cells can regulate trophoblast invasion and the remodeling of the decidua and spiral arteries by releasing cytokines and growth factors. Disruption of these processes due to dNK cell dysfunction may contribute to RPL [37]. Measuring the number and function of NK cells in peripheral blood and the uterus can help with RPL diagnosis and treatment.

2.5 Immune homeostasis at the maternal-fetal interface and reproductive success

Pregnancy starts with embryo implantation. A successful pregnancy depends on several factors, including a healthy embryo with strong growth potential and a suitable uterine environment with appropriate hormone levels [31]. Before implantation, estrogen and progesterone together prompt the endometrium to undergo decidualization. Once the blastocyst enters the uterine cavity, it can attach to the endometrium only during a brief window. At this time, endometrial stromal fibroblasts spontaneously differentiate into metaphase cells, while immune cells such as uterine NK cells and macrophages begin together. Several factors can disrupt decidualization and are linked to RPL. These include chronic endometrial inflammation, luteal insufficiency, obesity and endocrine disorders such as abnormal thyroid function [38, 39].

After implantation, the maternal-fetal interface forms a complex network of interactions between maternal and fetal cells. Fetal trophoblasts develop into syncytiotrophoblasts (STBs) and EVTs. Maternal decidual cells include decidual stromal cells (DSCs) and decidual immune cells (DICs). DICs make up about 40% of cells at the interface in early pregnancy. Their activity is closely regulated during implantation to support maternal tolerance of the fetal placenta. Immune imbalance at this site is also an important risk factor for RPL. Uterine NK cells, which form 70% of DICs, can recognize HLA-G on EVTs and become activated. They then release growth factors that support embryonic development [37, 40]. However, the link between uterine NK cell numbers and function and RPL remains unclear. Macrophages (10%-20%), T cells (10%-20%) and DCs also help maintain immune balance at the maternal-fetal interface [41, 42, 43]. Recent studies have shown that Tregs have a key role in pregnancy [44]. Immunosuppressive, tolerogenic DCs can prompt Treg development in the endometrium. Patients with RPL have fewer tolerogenic DCs, highlighting their role in maternal-fetal immune regulation [45].

Recent single-cell transcriptomic studies of the decidua have provided more detail on immune control at the maternal-fetal interface. They have identified new subsets of uterine immune cells and explored their possible links to RPL.

3. Maternal genetic factors in RPL

3.1 Maternal numerical and structural chromosomal abnormalities

Embryonic chromosomal aneuploidy is a leading genetic cause of pregnancy loss. It accounts for about 60% of sporadic spontaneous losses [46]. In a recent survey of 1,000 products of conception (POC), autosomal trisomies were the most common abnormalities (59.7%). These were followed by polyploidies (22%), monosomies (7.5%), structural chromosome rearrangements (7%) and multiple aneuploidies (3.8%) [47]. Most of these abnormalities arise from random errors during maternal meiosis I (MI), possibly due to abnormal chromosome segregation as oocytes develop. Older maternal age is generally linked to higher rates of embryonic aneuploidy during pregnancy [48]. Many studies have also linked embryonic chromosome abnormalities to RPL [47, 49]. However, compared with sporadic spontaneous pregnancy loss, women with RPL have a lower… embryonic chromosomal aneuploidy rates [50]. Recent studies estimate that 3.74%–9.88% of couples with recurrent pregnancy loss (RPL) carry structural or numerical chromosomal abnormalities [51, 52]. Balanced translocations are the most common, accounting for 38.00%–47.05% of abnormalities. Inversions account for 29.41%–34.70%, numerical abnormalities for 11.76%–16.50%, and Robertsonian translocations for 10.70%–11.76% [51–53]. Studies also show that female carriers are more common than male carriers among RPL couples with chromosomal aberrations [51, 54]. Women with RPL at advanced maternal ages also show consistently higher rates of aneuploidy [55, 56].

3.2 Maternal aneuploidy and chromosomal mosaicism

Maternal mosaicism may contribute to embryonic chromosomal aneuploidy, alongside random errors in the oocyte's first meiotic division and parental carriage of chromosomal aneuploidy [57]. Chromosomal mosaicism refers to the presence of genetically distinct cells within one individual. It can arise during embryonic development when chromosomes segregate during mitotic cell division. Robinson et al., reported recurring chromosomal abnormalities, including trisomies 15, 16 and 22, as well as triploidy, in eight RPL couples with normal karyotypes. Maternal mosaicism may have caused these findings [58].

Several groups have detected chromosomal aneuploidies in products of conception (POCs) from people with a history of RPL, despite normal fibroblast or lymphocyte karyotypes. Their findings suggest that maternal mosaicism is a likely source of embryonic chromosomal aneuploidies [59–62]. Ghevaria et al., [63] studied maternal aneuploidy mosaicism, or germline mosaicism, which may arise in primordial germ cells (gonadal mosaicism) or during premeiotic mitotic divisions of oogonia. They estimated that premeiotic aneuploidy occurs in more than 10% of unselected oocytes. Numerical abnormalities rarely recur. Maternal mosaicism should therefore be considered when parental karyotypes are normal and the same anomaly is observed more than once.

3.3 Maternal factors associated with genome stability in early embryonic cells

In RPL, embryonic chromosomal abnormalities may arise from parental carriage, maternal mosaicism or maternal age. Other factors may also contribute to embryonic or fetal aneuploidy, independent of these risks, and require further study in people with RPL. Burada et al. [64], for example, described a couple with three consecutive pregnancies affected by different trisomies. Neither partner had an abnormal karyotype or mosaicism. Delhanty et al. [65], found that some patients repeatedly produce embryos with mosaic aneuploidy during in vitro fertilization (IVF) cycles. These embryos divide chaotically. The findings suggest that maternal factors in oocytes may disrupt embryonic cell division, regardless of maternal age.

3.4 Maternal inherited thrombophilic factor variants

Researchers have examined inherited variants in three groups of thrombophilic factors: the factor V gene; enzymes involved in homocysteine metabolism (MTHFR, MTR and MTRR); and the prothrombin gene (PTG) [66, 67]. Factor V Leiden (FVL), a missense mutation in the factor V gene (p.R506Q), is the most studied thrombophilic variant in patients with RPL. Its frequency varies across populations, reaching 4.4% in Europe and 0.6% in Asia [68]. FVL can cause resistance to activated protein C (APC), leading to increased blood clotting [69]. However, its association with RPL remains disputed, with studies reporting both strong and no association [70–72]. Eslami et al. [73], conducted a large meta-analysis of 10,410 RPL cases and 9,406 controls. They found a significant association between FVL and RPL in the overall population, as well as in Asian, European and African populations, but not in South American populations.

The prothrombin G20210A mutation increases prothrombin mRNA and protein expression and is linked to a higher risk of thrombosis [74]. Liu et al., reviewed and analyzed 89 studies involving 30,254 people. Their findings showed that women carrying either the FVL or G20210A mutation had a higher risk of RPL [75]. Homocysteine (Hcy) is a sulphur-containing amino acid produced during methionine metabolism. Three main enzymes take part in this process: methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and methionine synthase reductase (MTRR). High Hcy levels are also regarded as a risk factor for thrombophilia [76]. Several common variants in these enzyme genes have been linked to higher plasma Hcy levels [77]. Hcy build-up in the mother may damage the endothelium and impair placental function. This may contribute to placental complications, including RPL, placental abruption and pre-eclampsia [78].

3.5 Maternal factors that affect immune responses

The fetus carries antigens inherited from the father and is therefore foreign to the maternal immune system, much like a semi-allograft [79]. Fetomaternal immune tolerance is essential for a healthy pregnancy. Research has examined several immune factors linked to RPL, including autoantibodies, peripheral and uterine NK cells, and regulatory T cells [80]. Genetic variants inherited from the mother that affect immune regulation have also been identified as RPL risk factors. The transcription factor

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Forkhead Box P3 (FOXP3) helps regulate the development of Treg cells and has been linked to RPL susceptibility [81, 82], a finding supported by a recent large-scale meta-analysis. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) limits T-cell activation and helps regulate T-cell responses and immune tolerance. Several studies have linked CTLA4 variants to RPL [83], [84], [85]. Programmed cell death 1 (PD1) and its ligand, PDL1, inhibit T-cell proliferation and cytokine production, acting as key negative regulators of T-cell activity [86]. Hayashi et al. [87] found that two PD1 variants (rs36084323 and rs3481962) were associated with a significant increase in RPL risk. Cho et al. [88] reported a positive association between RPL risk and complement factors D (CFD) and H (CFH), indicating a role for the complement system in pregnancy.

3.6 Whole-exome sequencing in women with RPL

Next-generation sequencing (NGS), particularly exome sequencing, is widely used to identify gene variants involved in human genetic diseases. To date, 14 studies have used exome sequencing to identify candidate genes and mutations that may contribute to RPL [89 -102]. Most examined RPL-associated mutations in women. In total, 66 candidate maternal genes and 12 paternal genes have been linked to RPL (Table 1). Only two genes, KHDC3L and CCNB3, were identified in two separate studies, pointing to the varied and complex causes of RPL. These genes were mainly linked to biological processes involving coagulation and angiogenesis, extracellular matrix (ECM) structure and breakdown, and immune regulation. The findings offer new insight into RPL pathogenesis, but functional studies are needed to establish how these variants contribute to RPL and support the development of targeted treatments.

Table 1: RPL-associated genes identified by whole-exome sequencing analysis

Groups	Biological processes	Maternal genes	Paternal genes
1	Coagulation and angiogenesis	ANXA5, F13A1, F5, FGA, FN1, THBS1, THBD, FLT1, ADAMTS1	KDR, ITGB1
2	Chromatin remodeling	BPTF	BPTF
3	Cell surface receptor	FGFR2, APP, EPS15, MS4A14	
4	DNA methylation	DNMT1, MECP2, MBD4	MECP2
5	DNA replication, RNA transcription and splicing	CBX3, NCOA1 CBX3, NCOA1	EFTUD2, POLR2B
6	DNA repair	REXO4, MSH2	
7	Extracellular matrix composition and degradation	COL6A3,TNC, MMP10, MMP9, LAMA2	
8	Immune regulation	FKBP4, TLR3, NLRP7, NLRP10, CR1,NFAM1, CSF1R, PSG9	
9	Mitosis	PK1, CENPH, PIF1, CEP250, CCDC68	PLK1,
10	Meiosis	CCNB3	
11	Membrane transporters	ABCA4, ABCB5, TCN2, CAPS, SLC2A7	

12	Membrane protein that mediates cell adhesion	TRO, CDH11, CDH1, YES1	
13	Metabolic process	FOXA2, IDO2, OSBPL5, GFA	
14	Oocyte maturation and Early embryonic development	KHDC3L, PADI6	
15	Transcription factors	BNC2, EPAS1, SOX21	SOX21
16	Others	AMN, BMP7, TRAF3IP1, LIFR, DNAH11, PLCD4, IFT122, AL078585.1	

4. Psychological Effects of Recurrent Miscarriage

Family is the foundation of society, particularly in traditional religious communities that value established family beliefs and roles [103-105]. In these cultures, a woman's role and status often depend on her ability to conceive and give birth to healthy children [105-107]. The repeated loss of a planned and wanted pregnancy can be deeply distressing [108]. Pregnancy loss has a major emotional and psychological effect on women and their partners [109-111]. These effects may include grief, guilt, fear of the future, conflict in relationships and communication, marital distress, and difficulty adapting [112-114]. The severity of these effects is linked to maternal age, the gestational age at loss, and the number of previous miscarriages [111]. Without suitable support, such experiences may lead to stress, depression, anxiety, or severe psychiatric illness [112,108,113]. Yet the effects of psychological factors on women's physical and reproductive health, and on the risk of further pregnancy loss, remain underestimated [107]. Some studies also identify psychological conditions as a possible primary cause of recurrent miscarriage [114,115].

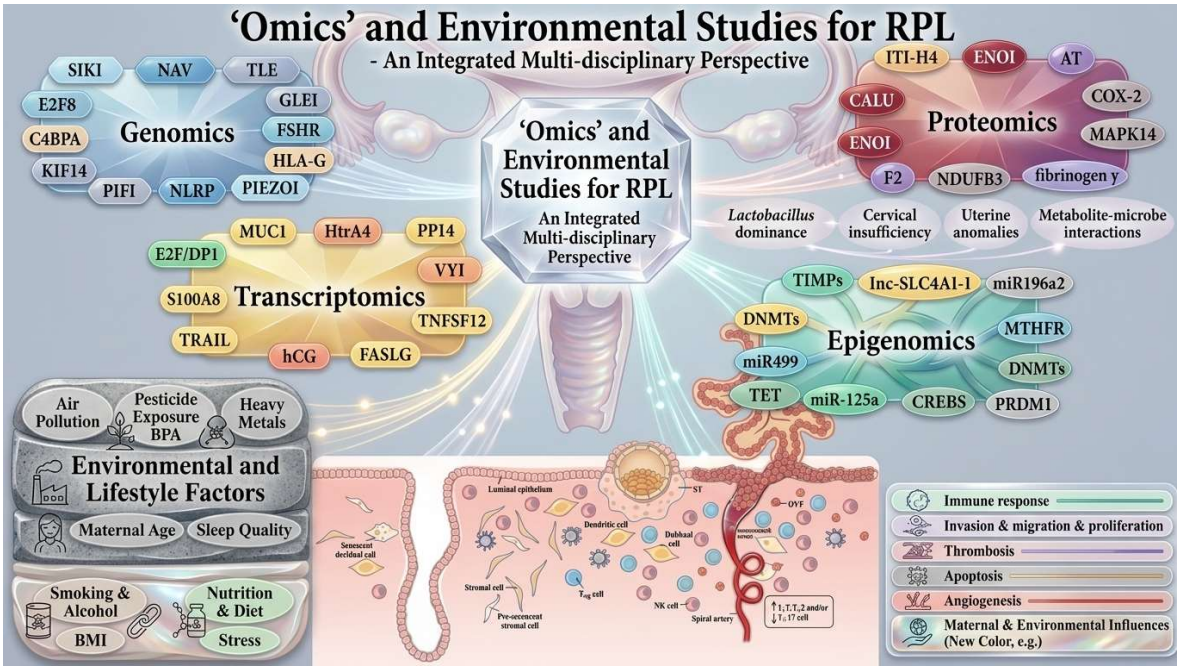
Research on the psychological health of women with RPL has found high levels of stress, depression, and anxiety [108,204,115-119]. These symptoms may raise the risk of another pregnancy loss [108,117].International guidelines for RPL care stress the value of psychological support for couples, which may help lower the risk of further losses [120-124]. However, few studies have assessed whether psychological interventions improve pregnancy outcomes for women and couples with RPL [121,125,126]. Most research relies on self-reported surveys and excludes male partners [127]. These limits understanding of how both partners experience repeated miscarriage.

Systematic reviews of cohort studies and randomized controlled trials suggest psychological support and interventions "may improve pregnant women's psychological well-being after miscarriage" [125]. Better well-being may also reduce poor outcomes in later pregnancies. A 2021 randomized controlled trial by Jensen et al. examined a tailored meditation and mindfulness intervention for women with RPL. The study found that a seven-week daily home programmed, combined with group sessions, reduced perceived stress more than standard supportive care [126].Reports on these interventions remain few, and psychological support services are scarce, especially in low-income settings. Further research and screening for mental health problems after RPL are needed to find effective ways to predict and prevent psychological illness [108,128]. Researchers and healthcare staff should include the psychosocial needs of couples with RPL in their care plans [109,126].

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5. Omics techniques in RPL

Figure (1)



6. Paternal chromosome abnormalities

Alongside genetic abnormalities in women, growing evidence shows that male factors, particularly genetic causes, contribute substantially to RPL [129]. In human embryos, paternal genome activation and subsequent zygotic genome activation (ZGA) occur at the 4–8-cell stage [130]. Genetic abnormalities in sperm, including variants of paternal origin, may therefore have little effect before ZGA but may disrupt later embryonic development or fetal development in the uterus. Numerical and structural chromosome abnormalities in sperm are major causes of embryonic death and RPL. They may arise de novo during spermatogenesis [131], leading to embryos with abnormal chromosome numbers or structures. Ramasamy et al. [132] found sperm aneuploidy in 40% of men with RPL whose sperm density and motility were normal. Sex chromosome aneuploidy in sperm was more common among men with abnormal sperm density and motility than among men with normal parameters (62% vs. 45%). Abnormal strict morphology, assessed using Kruger's strict criteria, was also strongly linked to higher rates of sperm aneuploidy.

A recent systematic review [133] found a significantly higher rate of sperm aneuploidy in men whose partners had a history of RPL. This broadly agrees with earlier studies [134], [135], [136]. A recent multicenter study also supports a possible role for sperm aneuploidy in unexplained RPL [137]. Chromosome abnormalities can also occur in carriers from couples affected by RPL or RM. Earlier studies [138, 139] found structural chromosome rearrangements in 2.7%–6.5% of couples with RPL, well above the estimated rate of about 0.5% in the general population [140]. Li et al. recently surveyed 3,235 couples with RPL and found structural or numerical chromosome abnormalities in 121 individuals (3.74%), comprising 75 women and 46 men [51]. Among 101 identified variants, balanced translocations were most common (46/101), followed by inversions (42/101), numerical abnormalities (20/101) and Robertsonian translocations (13/101). Dong et al. [141] used low-pass genome sequencing to assess chromosome abnormalities in 1,090 couples with RM. They found 127 abnormalities among 126 couples. Balanced translocations were also common in this group (61.9%, 78/126). Such translocations usually do not affect the carrier's physical traits, but errors during meiosis can lead carriers to produce genetically unbalanced gametes.

6.1 Sperm DNA fragmentation

Sperm DNA integrity is vital for fertilization and embryo development. Damage to sperm DNA, also known as sperm DNA fragmentation (SDF), may lower fertilization rates and cause embryonic arrest or pregnancy loss [142]. Fertilization by a sperm cell with DNA damage may increase damage to the embryonic genome, leading to problems at different stages of embryo or fetal development [143]. Robinson et al. [144], analyzed 16 cohort studies involving 2,969 couples. Their meta-analysis linked high levels of sperm DNA damage to a greater risk of sporadic miscarriage. Dai et al., assessed 19 studies involving 1,182 couples with unexplained RM and 1,231 couples without RM. Their meta-analysis found that higher SDF levels were significantly associated with unexplained RM, suggesting that SDF may contribute to its development [145]. Several large meta-analyses have also examined links between SDF and RPL. McQueen et al. included 579 men with a history of RPL and 434 male controls. Their findings showed a clear association between SDF and RPL [146]. Tan et al. analyzed 12 prospective and two retrospective studies, covering 530 men with a history of RPL and 639 fertile controls. Their results indicated that SDF provides diagnostic information beyond standard semen analysis and may be a paternal genetic factor in idiopathic RPL [147].

6.2 Y chromosome microdeletions

In 1995, Reijo et al. [148] first reported Y chromosome microdeletions, identifying them in 12 men with azoospermia. Deletions in this region, known as the azoospermia factor (AZF) or Deleted in Azoospermia (DAZ) region, are linked to impaired sperm production and male infertility. Further analysis divided the AZF locus into three sections: AZFa, AZFb and AZFc. Microdeletions in these regions can cause different degrees of impaired sperm production. Deletions in the overlapping AZFb/AZFc region may be linked to sperm counts ranging from no measurable sperm to normal levels [149].Several studies have examined links between Y chromosome microdeletions and RPL. Dewan et al. [149] first found that men from couples with RPL had a higher rate of microdeletions in the proximal AZFc region than men from fertile or infertile couples. Two later studies largely supported this finding [150, 151]. However, Dai et al. [152] examined 1,072 men with a history of RPL, alongside 971 infertile and 200 fertile controls, in Northeast China. They found no link between Y chromosome microdeletions and RPL. This result agrees with studies in Sri Lanka, Mexico and Iran [153], [154], [155].Several factors may explain these conflicting findings, including the choice of sequence-tagged site (STS) markers [152], whether DNA came from peripheral blood or sperm [155], and sample size [150]. More research and data are needed to clarify the role of Y chromosome microdeletions in the development of RPL.

6.3 Single gene variants of paternal origin

The link between maternal MTHFR C677T polymorphism and RPL risk has been studied extensively. Recent studies have also linked paternal C677T polymorphism to RPL etiology [156, 157]. Thrombophilia is widely recognized as a common RPL risk factor and is found in around 40%–50% of cases [158]. Ozdemir et al., found that paternal and maternal variants in thrombophilic genes, including FVL, FVR2, ACE and ApoE2, are associated with RPL [159].ANXA5 is an anticoagulant protein found in high levels in the human placenta and has also been linked to RPL. Bogdanova et al. [160] first found that carriers of the M2 haplotype in the ANXA5 promoter region had more than twice the risk of RPL compared with the general population. A recent large meta-analysis supports this finding [161]. Links between the ANXA5 M2 haplotype and RPL have also been reported in Japanese [162], Malay [163] and Indian populations [164], but not in Estonia or Denmark. Rogenhofer et al. [165] also found that the paternal ANXA5 M2 haplotype, like the maternal variant, was associated with RPL. These variants may also increase the risk of RPL. The ubiquitin pathway is involved in fertilization and embryo development. Variants in the USP26 (ubiquitin-specific peptidase 26) gene have been identified as risk factors for male infertility. Asadpor et al. [166] found that a USP26 haplotype containing the 370–371 insACA, 1423 C > T and 494 T > C mutations were significantly more common among men with a history of idiopathic RPL than among fertile men. This finding supports a role for paternal USP26 gene variants in the causes of RPL.

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7. Diagnosis and therapeutic management of RPL

7.1 Guidance on diagnosis and management of RPL

Current treatment recommendations for RPL mainly involve symptom-based care tailored to the underlying causes [31]. Several national and international societies have developed guidelines, including ESHRE, the Royal College of Obstetricians and Gynecologists (RCOG) [167], ASRM [1], the German Society of Gynecology and Obstetrics (DGGG), the Austrian Society of Gynecology and Obstetrics (OEGGG), and the Swiss Society of Gynecology and Obstetrics (SGGG) [168]. National guidelines do not fully agree on how RPL is defined and diagnosed, but their approaches to management are similar. Systematic testing for possible causes is recommended for patients with RPL. It is not generally recommended after a single miscarriage, unless there is a relevant family history or clinical evidence of an associated condition. Management and treatment are based on the underlying cause of RPL (Table 2).

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Table 2: Recommended management of women with recurrent pregnancy loss by cause

Etiology	Clinical testing	Therapeutic managements and Intervention	References
Genetic factors	Karyotype analysis of RPL couples and aborted embryo tissues	Genetic counseling before the next pregnancy PGT	[3]
Anatomical Structural Factors	Routine pelvic ultrasonography	Monitoring during pregnancy Hysteroscopic mediastinectomy is used for severe IUA Hysteroscopic myomectomy is used for submucosal fibroids Prophylactic cervical cerclage is recommended for cervical insufficiency	[3, 30]
Endocrine factors	Endocrine testing	Thyroxine management to keep the level of TSH controlled in an appropriate range. Exercises, oral hypoglycemic drugs and insulin injection for abnormal glucose metabolism Progesterone supplementation for LPD	
Prethrombotic state	Hereditary PTS screening and classical detection of aPLs excludes APS-related acquired PTS	Monotherapy or combination therapy of LMWH and LDA	[1, 49–52]
OAPS	Classical aPLs testing including LA, aCL, and	LDA combined with LMWH, plus HCQ or glucocorticoids if necessary	[3, 49–52]

	β2-GPIAb		
NOAPS	Individualized testing for nontypical aPLs profile	the managements were not unified. Existing treatments can still refer to the treatment of OAPS and need to be administered by experienced obstetricians and rheumatologists.	[3, 49,52]
Immune factors	ANAs and ENAs profile screening	Fertility counseling immunosuppressants, combined with LDA or LMWH if necessary	[3]
Infection Factors	Infection-related factors checking during Pregnancy	Appropriate antibiotic treatment for patients with obvious symptoms of genital tract infection. \	[3]
Other factors	Recording clinical information of RPL couples	Keep good lifestyle habits and stay away from adverse environments	[3]

LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; HCQ, hydroxychloroquine; IUA, intrauterine adhesion; LPD, luteal phase deficiency; OAPS, obstetrical antiphospholipid syndrome; NOAPS, non-criteria obstetrical antiphospholipid syndrome; RPL, recurrent pregnancy loss; PTS, prethrombotic state; aPLs, antiphospholipid antibodies; ANAs, antinuclear antibodies; LA, lupus anticoagulant; aCL, anticardiolipin antibody.

8. Novel strategies for managing RPL

Alongside standard care for patients with a known cause of RPL, several new treatments are being studied. Some studies report that multivitamin supplements, particularly vitamin D, may benefit patients with RPL. However, the doses used vary between studies [169], [170], [171]. Immunotherapy has also been studied extensively, leading to the use of several treatments in clinical practice. These include lymphocyte immunotherapy (LIT), anti-tumor necrosis factor (TNF) alpha agents, granulocyte colony-stimulating factor (G-CSF) and paternal cell immunization [172], [173], [174]. However, some studies indicate that treatments such as intravenous immunoglobulin G (IVIG) do not increase live birth rates in patients with RPL [3, 183]. Meta-analyses and randomized controlled trials (RCTs) also suggest that immunomodulatory agents may benefit certain RPL subgroups [175], [176], [177], [178]. Current consensus recommends that immunotherapy be used only in clinical research. Therapeutic intralipid infusions and endometrial scratching have also been assessed, but studies have found no benefit for RPL [2, 44].

Several groups have studied mesenchymal stem cell (MSC) therapy in abortion-prone mouse models. Their findings suggest that MSC treatment can improve pregnancy outcomes by altering immune responses at the maternal-fetal interface [179]. Eskandarian et al. found that MSC therapy reduced the abortion rate in these mice, possibly by increasing the frequency of uterine dendritic cells (uDCs) [180]. Kahmini et al. injected adipose-derived MSCs into abortion-prone mice. Their results suggest that MSCs may improve the tolerogenic environment at the maternal-fetal interface by reducing the infiltration of CD49b+ NK cells into the decidua [181]. Farrokhi et al., found that MSC therapy reduced abortion rates by promoting Treg expansion and increasing the

expression of Treg-related genes [182]. Xiang et al. also reported that injecting MSC-derived exosomes into the uterine horns altered T-cell and macrophage responses at the maternal-fetal interface, reducing abortion rates in abortion-prone mice [179]. These findings point to new possibilities for developing treatments to improve pregnancy outcomes in patients with RPL.

9. Recent advances in the treatment of unexplained RPL

Unexplained RPL (URPL) is diagnosed by exclusion. Patients must first meet the diagnostic criteria for RPL, while autoimmune disease, PTS, reproductive tract abnormalities, endocrine disorders, and chromosomal or genomic abnormalities must be ruled out. Some studies suggest that URPL may have a genetic basis [183] and may also involve unknown immune factors. Meta-analyses have identified several genes associated with idiopathic or unexplained RPL, suggesting that genetic factors may contribute to URPL. Many of these genes are linked to key biological processes, including immune responses, coagulation, metabolism, angiogenesis [184, 185] and placental function. Evidence also links immune factors to URPL. van der Zwan et al. found that changes in the proportion of a small activated subset of dDC cells, along with cytotoxic CD8+ T cells, may contribute to URPL [42]. Svensson-Arvelund et al., also found that a high M1/M2 macrophage ratio may be linked to URPL pathogenesis [41].

Clinical management of URPL remains challenging because evidence is limited. Routine use of IVIG [186], [187], [188], liposomes, LIT, anticoagulant therapy (LDA or LMWH), glucocorticoids, cyclic cyclosporine A (CsA), G-CSF, TNF-α inhibitors and other treatments is not recommended [2]. Patients with unexplained RPL should be encouraged to take part in clinical research programs suited to their circumstances. Identifying the genetic factors that cause URPL may help guide the development of new treatments.

I. Conclusion

This review summarizes current knowledge and recent advances in the causes, diagnosis and treatment of RPL. These findings offer new insight into the origins of pregnancy loss and may help guide the development of treatments for women with RPL. Although the field has advanced, the cause of pregnancy loss remains unclear for more than half of patients with RPL. Effective treatments for these patients are limited, largely because the mechanisms underlying URPL are not well understood. Many international guidelines recommend supportive care for couples with unexplained RPL [189]. Future studies should focus on these patients to improve pregnancy outcomes. New technologies may help identify the causes of URPL in individual patients. For example, single-cell RNA sequencing of pregnancy-related tissues, alongside studies of patient-specific endometrial [190] and placental organoids [191], may help identify the factors involved in URPL for specific couples. Such findings could also guide the development of personalized treatments.

Many genetic factors that may predispose people to RPL have been identified (Figure 2). As noted above, RPL-associated genes fall into several functional groups, including those linked to chromosomal abnormalities, thrombosis and immune responses. Studies suggest that identifying genetic variants in people with recurrent spontaneous abortion (RSA), particularly unexplained cases, may help explain the causes of RPL [185, 192]. Interactions between genetic and environmental factors also play a key role in the causes of many human diseases [193]. Few large-scale studies have examined how RPL susceptibility genes interact with environmental factors. The interaction between MTHFR gene variants and folic acid supplements has been studied extensively, and this gene-nutrient interaction affects several pregnancy complications [194]. Future research on the combined effects of environmental risk factors and genetic variants may clarify the causes of RPL. Genetic factors inherited from both parents contribute to recurrent pregnancy loss (RPL). Studies have linked RPL to several genetic factors, including chromosomal abnormalities inherited from either parent, maternal aneuploidy mosaicism, sperm DNA fragmentation, Y chromosome microdeletions, and variants in functional genes involved in coagulation, immune responses and extracellular matrix (ECM) remodeling. Next-generation sequencing (NGS), including whole-exome sequencing [195, 196], is widely used to identify genetic causes of inherited disorders, including RPL. More than 14 studies have examined mutations that may cause RPL (Table 1). These studies have found rare, disease-associated variants in several genes, offering new insight into RPL pathogenesis and possible explanations for some patients' recurrent losses. However, the causal role of most variants remains unknown. Further work using cell and animal models could test their functional effects. NGS can also support clinical diagnosis [197] and has

advantages over conventional cytogenetic testing. Dong et al. found that low-pass genome sequencing detected more chromosomal abnormalities than standard karyotype analysis in an RPL population [141]. Clinical research and laboratory studies are both needed to improve understanding of RPL and develop ways to improve outcomes for people affected by this complex condition.

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