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Review Article

The Importance of Prenatal Diagnosis in The Investigation of Recurrent Pregnancy Loss: A Transition from Screening to Diagnostics

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Abstract
Recurrent pregnancy loss (RPL) is a complex reproductive health disorder affecting a significant proportion of women of reproductive age and is associated with considerable psychological, social, and economic burdens. In approximately 50% to 75% of cases, the etiology of RPL remains idiopathic, despite substantial advances in reproductive medicine. This review aims to synthesize current evidence on the etiological factors contributing to RPL and to evaluate the role of prenatal diagnostic approaches in its investigation and management. Key contributing factors discussed include genetic, anatomical, endocrine, immunological, thrombophilic, and environmental influences. In addition, recent advances in both non-invasive and invasive prenatal diagnostic techniques are explored, including chromosomal microarray analysis, whole-exome sequencing, parental karyotyping, and preimplantation genetic testing. The role of genetic counseling is also emphasized as an essential component in supporting clinical decision-making and enhancing patient understanding. By integrating advanced diagnostic technologies with a multidisciplinary clinical approach, prenatal diagnostics provide critical insights into underlying disease mechanisms and enable more individualized management strategies. This review highlights the importance of comprehensive evaluation and appropriate counseling to improve reproductive outcomes and reduce the emotional and financial burden experienced by affected couples.

Keywords: *Chromosomal microarray analysis; genetic testing; genetic counseling; prenatal diagnosis; recurrent pregnancy loss.*
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INTRODUCTION

The Indonesian Society of Reproductive Endocrinology and Fertility–Indonesian Obstetrics and Gynecology Association (HIFERI–POGI) defines recurrent pregnancy loss (RPL) as the occurrence of at least two consecutive miscarriages at a gestational age of less than 20 weeks and/or a fetal weight of less than 500 grams.[1] Similarly, the American Society for Reproductive Medicine (ASRM) defines RPL as two or more failed clinical pregnancies confirmed by ultrasonography or histopathological examination of pregnancy tissue. RPL is a relatively common reproductive health problem, affecting approximately 1–2% of couples of reproductive ages worldwide.[2,3] Existing literature has identified a wide range of contributing factors, including genetic abnormalities, maternal age, uterine anomalies, immunological and thrombotic disorders, endocrine imbalances, infections, as well as paternal and lifestyle-related factors. However, in approximately 50% to 75% of cases, the etiology of RPL remains idiopathic.[4]

RPL affects not only physical health but also has profound emotional consequences. Couples experiencing recurrent miscarriage often endure significant psychological distress, including prolonged grief, anxiety, depression, and symptoms consistent with post-traumatic stress disorder (PTSD). The severity of this distress is often proportional to the number of pregnancy loss episodes experienced and may adversely affect interpersonal relationships,

including partner dynamics and social interactions. Furthermore, limited public awareness and inadequate social support may exacerbate this psychological burden.[5] Therefore, a holistic approach that integrates psychological support and counseling is essential and should be considered as important as medical management.[6]

In addition to psychological impacts, RPL also imposes substantial economic burdens. The costs associated with repeated diagnostic evaluations, long-term treatment, and assisted reproductive technologies such as in vitro fertilization (IVF) and preimplantation genetic testing (PGT) can be considerable, placing significant financial strain on affected couples.[7] Given the high proportion of unexplained cases and the multifactorial nature of RPL, there is a critical need for more precise and comprehensive diagnostic approaches. Prenatal diagnosis is essential for identifying underlying genetic and chromosomal abnormalities that may not be detected through conventional evaluation. Advanced diagnostic techniques, including chromosomal microarray analysis, whole-exome sequencing, and other molecular approaches, provide deeper insights into the etiology of pregnancy loss and help reduce the proportion of idiopathic cases. Moreover, prenatal diagnosis can guide clinical decision-making, enable risk stratification, support personalized management strategies, and improve counseling for future pregnancies. Therefore, a comprehensive review of current evidence regarding prenatal diagnostic approaches in RPL is essential to better understand its clinical utility and to optimize patient outcomes.

ETIOLOGY OF RECURRENT PREGNANCY LOSS

The etiology of RPL is multifactorial, involving a complex interplay of genetic, anatomical, endocrine, immunological, thrombophilic, and environmental and lifestyle factors. These diverse contributors may act independently or synergistically to disrupt normal implantation and pregnancy progression, thereby increasing the risk of miscarriage.

Genetic Factors

Genetic abnormalities are among the most common causes of RPL. Embryonic chromosomal abnormalities, particularly aneuploidy (such as trisomy or monosomy X), are usually de novo and occur spontaneously rather than being inherited. Aneuploidy accounts for about 50% of miscarriages, especially in the first trimester.[4,8,9] In addition, parental chromosomal abnormalities, including balanced translocations such as Robertsonian translocations, may also contribute to RPL.[10]

Balanced translocations involve the exchange or rearrangement of chromosomal material without a net loss or gain, so affected individuals are typically phenotypically normal. Reciprocal translocations occur between non-homologous chromosomes, while Robertsonian translocations involve the fusion of acrocentric chromosomes, resulting in a total of 45 chromosomes. Other structural abnormalities, such as chromosomal inversions, are also associated with RPL and are more prevalent among affected patients than in the general population (2.28% vs. 1%).[11]

When one partner carries a balanced translocation, the risk of miscarriage increases by approximately 20–40% due to the possibility of forming unbalanced gametes, which may lead to nonviable embryos or offspring with congenital anomalies.[12,13] Overall, chromosomal abnormalities are identified in around 3.74% to 9.88% of couples with RPL, with balanced translocations accounting for a substantial proportion of these cases.[11]

Additionally, hyperhomocysteinemia, often caused by polymorphisms in the MTHFR gene affecting folate metabolism, is recognized as a risk factor for RPL. Elevated homocysteine levels can lead to vascular inflammation, placental damage, and impaired uterine blood flow, ultimately increasing the risk of thrombosis and pregnancy loss.[14]

Anatomical Factors

Structural abnormalities of the uterus can disrupt processes such as embryo implantation and early pregnancy development, thereby increasing the risk of miscarriage. These abnormalities often arise from impaired development or fusion of the Müllerian ducts during embryogenesis. As a result, a spectrum of congenital uterine anomalies may occur, including septate, bicornuate, or unicornuate uterus, as well as Müllerian agenesis. The clinical impact of these anomalies varies depending on the timing and extent of developmental disruption, ranging from mild structural variations that may be asymptomatic to severe malformations involving the complete absence of the uterus, cervix, and fallopian tubes, all of which can significantly compromise reproductive outcomes.[4,6]

Endocrine Factors

Disorders of the endocrine system can significantly affect fertility and pregnancy outcomes. Conditions such as poorly controlled diabetes mellitus, thyroid dysfunction (hypothyroidism or hyperthyroidism), and hyperprolactinemia can disrupt the hormonal balance needed for normal reproductive processes. This imbalance may impair implantation and placental development, ultimately increasing the risk of miscarriage. [4,6,7]

Immunological Factors

Antiphospholipid syndrome (APS) is a well-established cause of recurrent miscarriage. In APS, the immune system produces abnormal antibodies against phospholipids, which are essential components of cell membranes. This immune response promotes thrombosis within placental vessels, leading to placental insufficiency and subsequent pregnancy loss.[15]

Thrombophilic Factors

Thrombophilia, whether inherited or acquired, is characterized by an increased tendency for abnormal blood clot formation and has been implicated as a contributing factor in recurrent pregnancy loss. Common hereditary conditions include mutations such as Factor V Leiden and prothrombin G20210A, which

promote a hypercoagulable state. These abnormalities can impair uteroplacental circulation by promoting microthrombus formation within placental vessels, leading to reduced maternal-fetal blood flow and compromised nutrient and oxygen delivery. As a result, placental function may be disrupted, adversely affecting fetal development and increasing the risk of miscarriage.[6,16]

Environmental and Lifestyle Factors

Environmental and lifestyle factors are increasingly recognized as important contributors to RPL. Modifiable exposures such as smoking, excessive alcohol consumption, high caffeine intake, and obesity have been consistently associated with an elevated risk of miscarriage through mechanisms including oxidative stress, hormonal dysregulation, impaired endometrial receptivity, and placental dysfunction. Obesity, in particular, is linked to chronic low-grade inflammation and metabolic disturbances that may adversely affect implantation and early embryonic development.[17] In addition to maternal factors, paternal influences are also gaining attention; compromised sperm quality, especially increased sperm DNA fragmentation, has been associated with impaired fertilization, abnormal embryogenesis, and a higher likelihood of pregnancy loss. Environmental toxins, occupational exposures, and unhealthy lifestyle habits in males may further exacerbate sperm DNA damage, highlighting the importance of evaluating both partners in the assessment and management of RPL.[15]

ROLE OF PRENATAL TESTING AND DIAGNOSIS

Since the 1980s, prenatal testing, both screening and diagnostic, has played an important role in reducing the incidence of congenital abnormalities. Various modalities are employed to detect fetal anomalies, including ultrasonography, serological testing, invasive prenatal procedures, and non-invasive prenatal testing.[18]

Prenatal diagnosis is strongly recommended as part of the evaluation of recurrent pregnancy loss, as it enables the identification of underlying genetic and chromosomal abnormalities that may not be apparent through routine assessment. It provides valuable prognostic information that can help predict pregnancy outcomes and supports informed clinical decision-making in determining appropriate management strategies. A comprehensive evaluation of women with RPL should therefore prioritize the identification of both underlying etiologies and modifiable risk factors, allowing clinicians to develop more effective, targeted, and individualized approaches to patient care and future pregnancy planning.[15]

NON-INVASIVE PRENATAL TESTING

Non-invasive prenatal testing (NIPT) is a screening method that utilizes next-generation sequencing (NGS) of cell-free DNA (cfDNA) to identify genetic variants representing chromosomal abnormalities. Cell-free DNA originates primarily from placental trophoblasts and circulates in the maternal bloodstream, allowing detection in maternal plasma as early as 10 weeks of gestation. Its concentration declines rapidly after placental delivery. This biological characteristic makes cell-free fetal DNA (cffDNA) a valuable biomarker for the early detection of chromosomal aneuploidy during pregnancy.[18,19]

Two principal analytical approaches are used in NIPT: genome-wide NIPT, which analyzes cfDNA from all chromosomes, and targeted NIPT, which focuses on specific chromosomes, such as in triploid screening.[20] Not all genetic conditions can be detected using NIPT. When genetic disorders or congenital anomalies are suspected based on ultrasonographic findings, medical history, or clinical examination, genetic counseling and confirmatory prenatal diagnostic testing should be considered.

NIPT is widely used for screening common autosomal aneuploidies, including Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), and Down syndrome (trisomy 21).[20] Multiple studies have demonstrated high detection accuracy for these conditions. A review by Siva et al. reported that NIPT is reliable for detecting trisomy 13, 18, and 21, with sensitivities exceeding 90% and specificities above 99%. NIPT also demonstrates high positive predictive values (PPVs) and low false-positive rates for trisomy detection in both singleton and twin pregnancies.[19]

In addition, NIPT may be used to screen for sex chromosome aneuploidies, including Turner syndrome (monosomy X), Klinefelter syndrome (47,XXY), triple X syndrome (47,XXX), and Jacobs syndrome (47,XYY). However, the PPVs for sex chromosome abnormalities are generally lower than those for autosomal aneuploidies. This limitation is partly attributable to biological factors such as confined placental mosaicism.[20]

NIPT may also be applied to screen for rare autosomal aneuploidies. However, these conditions are frequently associated with early pregnancy loss. Therefore, positive findings require confirmatory testing, as results may reflect confined placental mosaicism or true fetal mosaicism.[20]

Segmental aneuploidies, which are defined as chromosomal deletions or duplications of 7 Mb or larger, are known to be associated with fetal structural anomalies. These chromosomal abnormalities can affect normal fetal development and may contribute to adverse pregnancy outcomes.[9] In cases where one or both parents are suspected carriers of balanced translocations, NIPT may be considered as a preliminary prenatal screening tool.[21]

The use of NIPT for detecting microdeletions and microduplications remains controversial. Critics argue that low PPVs, high false-positive rates, and uncertain clinical significance of some copy number variants (CNVs) complicate clinical management.[22] In contrast, proponents emphasize that the primary goal of prenatal screening is to reduce the incidence of chromosomal disorders and therefore support the inclusion of microdeletion and microduplication screening despite limited accuracy.[18]

Recently, an advanced version known as NIPT-plus has been introduced. In a study by Xue et al., NIPT-plus demonstrated a PPV of 80% for detecting 22q11.2 microduplication syndrome, 75% for

DiGeorge syndrome, and 50% for Prader–Willi/Angelman syndrome and Cri-du-chat syndrome.[18]

NIPT results are generally reported as probabilities, with high-risk results indicating an increased likelihood of specific chromosomal abnormalities and low-risk results suggesting reduced probability. However, as NIPT is a screening modality, its findings are not diagnostic and must be confirmed by invasive procedures such as amniocentesis or chorionic villus sampling (CVS).[20]

Several factors may influence NIPT accuracy, including low fetal fraction, advanced maternal age, high maternal body mass index, early gestational age at testing, confined placental mosaicism, vanishing twin syndrome, maternal chromosomal abnormalities, and maternal malignancy.[19] It should also be noted that NIPT cannot detect fetal structural abnormalities. When genetic abnormalities are suspected based on ultrasound findings or family history, genetic counseling and targeted prenatal diagnostic testing are strongly recommended.

In a meta-analysis, Thomas Liehr reported a substantial number of false-positive NIPT results that were only identified after pregnancy termination.[23] Furthermore, a study in Japan found that 98% of pregnant women who underwent NIPT avoided invasive diagnostic procedures.[19] Inadequate pre- and post-test counseling contributes to misconceptions that NIPT is a diagnostic tool rather than a screening method, underscoring the importance of comprehensive genetic counseling in clinical practice.

INVASIVE PRENATAL DIAGNOSIS

Invasive prenatal diagnosis consists of two primary tissue-sampling procedures: CVS and amniocentesis. CVS is typically performed between 11 to 14 weeks of gestation, whereas amniocentesis is usually conducted between 15 to 20 weeks of gestation.[24] In addition, guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) and ASRM recommend cytogenetic analysis of products of conception (POC).[12] In pregnant women with a history of recurrent pregnancy loss or those with high-risk factors, invasive prenatal testing may be considered for comprehensive evaluation.[25] Both CVS and amniocentesis are associated with procedural risks, including an increased risk of limb defects when CVS is performed before 10 weeks of gestation, procedure-related miscarriage (approximately 1% for CVS and 0.25%–0.5% for amniocentesis), and the potential for intrauterine infection following the procedure.[8,18]

Following CVS or amniocentesis, tissue samples are analyzed in the laboratory. The most performed analysis is conventional karyotyping. Karyotyping enables visualization of fetal chromosomes but has limited resolution and is unable to detect small-scale chromosomal abnormalities such as microdeletions, microduplications, or single-gene mutations.[26]

CHROMOSOMAL MICROARRAY ANALYSIS

Chromosomal microarray analysis (CMA), including array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) microarrays, has emerged as a preferred alternative and has largely replaced conventional karyotyping in many clinical settings. CMA provides substantially higher resolution, allowing detection of not only aneuploidies but also small CNVs, such as submicroscopic deletions and duplications that are undetectable by standard karyotyping.[8] CMA can identify CNVs as small as 50–100 kb.[27]

Clear and definitive CMA results enable more accurate prognostic counseling and may reduce the need for unnecessary additional testing when an underlying cause is identified. When embryonic abnormalities are detected, clinicians may focus on preimplantation genetic testing for aneuploidy (PGT-A) or provide counseling regarding future RPL risk. Conversely, if the embryo is found to be euploid, further evaluation can be directed toward maternal or paternal contributing factors. This targeted approach enhances diagnostic efficiency while simultaneously reducing emotional and financial burdens for patients.

A major limitation of CMA is its inability to detect point mutations or single-gene disorders, restricting its utility in diagnosing a broad spectrum of monogenic diseases.[25] CMA is recommended for fetuses with one or more structural abnormalities identified by ultrasonography and for patients undergoing invasive prenatal diagnosis. However, CMA cannot detect balanced chromosomal rearrangements, such as balanced translocations, because no net gain or loss of chromosomal material occurs.[8,27]

WHOLE EXOME SEQUENCING

Advances in genetic technologies have rapidly expanded diagnostic capabilities, and NGS and whole-exome sequencing (WES) are increasingly utilized in the evaluation of recurrent pregnancy loss. NGS, which enables high-throughput parallel DNA sequencing at progressively lower costs, demonstrates superior diagnostic performance compared with conventional G-banding karyotyping, particularly in miscarriages occurring before 12 weeks of gestation.[28]

WES examines all protein-coding regions of the genome and has demonstrated strong potential in identifying monogenic disorders associated with pregnancy loss. This method provides broader diagnostic coverage and improves the ability to detect rare genetic variants that may contribute to RPL.[29]

WES is particularly useful for identifying point mutations, small insertions and deletions, as well as certain structural variants related to monogenic and syndromic conditions. Compared with conventional cytogenetic techniques, WES offers higher resolution and a greater diagnostic yield, making it a valuable tool in the genetic evaluation of RPL.[26]

PARENTAL KARYOTYPE ANALYSIS

Parental karyotype analysis in both partners represents one of the initial and fundamental diagnostic steps in the evaluation of recurrent pregnancy loss. This examination aims to detect balanced structural chromosomal abnormalities, including reciprocal and Robertsonian translocations, as well as mosaicism that may be present in one or both parents.[12,15]

Balanced translocations occur when segments are exchanged between two different chromosomes or when an entire chromosome attaches to another chromosome, as in Robertsonian translocation. Although carriers of balanced translocations are generally asymptomatic and do not exhibit clinical manifestations due to the absence of net genetic gain or loss, they have an increased risk of producing unbalanced gametes during meiosis.[12] These unbalanced gametes, when involved in fertilization, may result in nonviable embryos or fetuses with severe congenital anomalies or intellectual disabilities, frequently leading to spontaneous miscarriage.[11]

Studies have estimated that structural and numerical chromosomal abnormalities are detected in approximately 3.74% to 9.88% of couples with RPL. Among these, balanced translocations account for 38% to 47.05% of cases, followed by inversions (29.41%–34.70%), numerical abnormalities (11.76%–16.50%), and Robertsonian translocations (10.70%–11.76%).[12] Identification of couples carrying balanced translocations is clinically important, as it enables direct recognition of the underlying genetic cause of RPL.

Interestingly, several studies have reported that among couples with RPL and chromosomal abnormalities, female carriers are more prevalent than male carriers. However, in addition to chromosomal factors, advanced maternal age also contributes significantly to the increased incidence of embryonic aneuploidy.[12]

PREIMPLANTATION GENETIC TESTING

Preimplantation genetic testing (PGT) involves genetic analysis of embryos generated through IVF prior to uterine transfer. The primary objective of PGT is to determine the genetic status of embryos, allowing only genetically normal or unaffected embryos to be selected for transfer.[23] Three main types of PGT are currently applied in clinical practice:[30]

PGT for Aneuploidy (PGT-A)

PGT-A aims to identify euploid embryos with a normal chromosomal complement. PGT-A is commonly recommended for couples with specific risk factors, including advanced maternal age (AMA), which is associated with a higher incidence of aneuploid embryos, recurrent implantation failure (RIF), severe male factor infertility that may compromise embryo quality, and idiopathic RPL in the presence of normal parental karyotypes.[31]

PGT for Monogenic Disorders (PGT-M)

PGT-M is a specialized technique used to identify embryos that carry specific inherited genetic mutations before implantation. This method is particularly useful for couples who are known carriers of single-gene disorders, as it allows the selection of embryos that are free from the disease-causing mutation. By doing so, PGT-M helps prevent the transmission of genetic conditions to offspring and reduces the risk of pregnancy loss related to these disorders. PGT-M is commonly applied in conditions such as Huntington's disease, thalassemia, cystic fibrosis, and other inherited monogenic disorders. The procedure is typically performed in conjunction with IVF, where embryos are biopsied at an early stage of development and genetically analyzed.[32]

PGT for Structural Rearrangements (PGT-SR)

PGT-SR is specifically indicated for couples who are carriers of balanced reciprocal or Robertsonian translocations or chromosomal inversions. The primary objective of PGT-SR is to identify and select embryos with balanced or normal chromosomal configurations, thereby reducing the risk of miscarriage associated with unbalanced chromosomal segregation. By enabling the selection of viable euploid embryos or embryos unaffected by structural chromosomal abnormalities, both PGT-A and PGT-SR play an important role in addressing major genetic contributors to RPL. These approaches significantly reduce the likelihood of miscarriage related to embryonic chromosomal abnormalities and improve overall reproductive outcomes.[33]

ROLE OF GENETIC COUNSELORS

Genetic counseling plays an important role in the management of recurrent pregnancy loss. According to ASRM guidelines, genetic counseling represents an initial and essential approach in the care of patients with RPL.[26] During the pre-test counseling phase, genetic counselors obtain comprehensive family and medical histories documented in pedigree charts, provide detailed explanations of potential etiologies of RPL, describe available diagnostic testing options, and facilitate discussions regarding the risks and benefits of each test.[6]

Genetic counselors assist couples in understanding the purpose, benefits, and limitations of available diagnostic procedures through a non-directive approach, in which balanced information is provided to support informed decision-making in accordance with patients' values and preferences without imposing personal judgments. In the context of RPL, prenatal diagnosis constitutes a key step in evaluation, as it enables the identification of genetic or chromosomal abnormalities in an ongoing pregnancy, provides important prognostic information, and guides subsequent clinical management; accordingly, guidelines from the RCOG and ASRM recommend cytogenetic analysis of POC following miscarriage.[26,28]

As previously discussed, the two main invasive prenatal diagnostic procedures are CVS and amniocentesis. These techniques allow direct genetic analysis of fetal tissue and enable detection of chromosomal abnormalities such as aneuploidy. However, conventional karyotyping has limited resolution and cannot identify small-scale chromosomal abnormalities, including microdeletions and microduplications.[22,26] This limitation shows the

importance of advanced technologies such as CMA and WES. CMA provides higher resolution and enables detection of copy number variants CNVs that are undetectable by conventional karyotyping. Meanwhile, WES analyzes protein-coding regions of the genome and facilitates the identification of monogenic disorders and rare genetic variants that may contribute to RPL.

In addition to pre-test counseling, genetic counselors are responsible for communicating laboratory results, diagnoses, and long-term follow-up plans during post-test counseling sessions. Counselors assist couples in interpreting complex information, including uncertain results such as variants of uncertain significance (VUS) and incidental findings that may not be directly related to RPL but have potential long-term health implications. They serve as an essential link between medical information and patient comprehension, supporting informed decision-making and ensuring accurate understanding.

Despite extensive research on RPL, more than 50% of cases remain without an identifiable cause, commonly referred to as unexplained recurrent spontaneous abortion (URSA).[12] In cases where prenatal diagnostic results are negative and no genetic etiology is identified, supportive counseling is particularly important. Counselors should demonstrate empathy, strong listening skills, and sensitivity to patients' reproductive histories and emotional experiences.[25]

Recurrent pregnancy loss imposes a substantial emotional burden on affected women and their partners, including grief, anxiety, depression, and symptoms consistent with PTSD. Healthcare providers and genetic counselors are therefore encouraged to screen for depressive symptoms in patients with a history of RPL. When necessary, referrals to mental health services or support groups should be provided.[6] Genetic counselors may serve as intermediaries in facilitating access to such support networks.

CONCLUSION

Recurrent pregnancy loss is an important clinical condition affecting a small but clinically significant proportion of couples, estimated at approximately 1–2% worldwide, and is associated with multifactorial etiologies, although a substantial proportion remains unexplained. Beyond its physical impact, RPL also imposes considerable psychological and economic burdens on affected couples. In this context, prenatal diagnosis plays a pivotal role in identifying underlying genetic and chromosomal abnormalities that may not be detected through conventional evaluation. Advanced diagnostic approaches, including chromosomal microarray analysis and whole exome sequencing, enhance etiological detection, reduce the proportion of idiopathic cases, and support more accurate prognostic assessment. These modalities facilitate informed clinical decision making, enable risk stratification, and guide personalized management and counseling for future pregnancies, ultimately contributing to improved reproductive outcomes.

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