GENETIC ASPECTS AND DIAGNOSIS OF EARLY PREGNANCY LOSS

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Annotation. *Early pregnancy loss (EPL) is a prevalent reproductive complication, with genetic abnormalities being a leading cause. This article reviews the genetic factors contributing to EPL, focusing on chromosomal abnormalities, single-gene mutations, and maternal genetic predispositions. It further explores current diagnostic techniques including conventional karyotyping, chromosomal microarray analysis, and molecular genetic testing, emphasizing their role in accurate diagnosis and clinical management. Understanding these genetic aspects is essential for effective genetic counseling, risk assessment, and improving reproductive outcomes for affected couples.*

Keywords: *miscarriage, genetic abnormalities, chromosomal abnormalities, aneuploidy, chromosomal microarray analysis, karyotyping, genetic diagnosis, recurrent miscarriage, genetic counseling.*

Introduction. Early pregnancy loss (EPL), defined as the spontaneous loss of a pregnancy before 20 weeks of gestation, is a common complication that affects approximately 10-20% of clinically recognized pregnancies worldwide. While the experience of miscarriage is emotionally distressing for patients and families, it also presents a significant clinical challenge for healthcare providers due to the complexity and multifactorial nature of its underlying causes. Among these, genetic factors stand out as one of the most prevalent and well-studied contributors to EPL.

The early stages of embryonic development are highly sensitive to genetic disruptions, and abnormalities in the fetal genome often result in developmental arrest, leading to miscarriage. Genetic causes of EPL include chromosomal abnormalities, such as aneuploidies and structural rearrangements, as well as single-gene mutations and maternal genetic predispositions. These abnormalities can interfere with normal embryogenesis, implantation, and placental development, all of which are essential for a successful pregnancy.

Understanding the genetic basis of early pregnancy loss not only aids in elucidating the pathophysiology behind miscarriage but also plays a crucial role in guiding diagnostic workups and clinical management. Advances in genetic testing technologies, from conventional karyotyping to chromosomal microarray analysis and next-generation sequencing, have dramatically improved our ability to detect and characterize genetic anomalies associated with miscarriage. This progress has important implications for genetic counseling, risk assessment, and the development of personalized therapeutic

strategies aimed at preventing recurrent losses. This article aims to provide a comprehensive overview of the genetic factors involved in early pregnancy loss and discuss the current diagnostic methodologies used to identify these causes. Through a better understanding of the genetic aspects and their clinical implications, clinicians and researchers can enhance patient care and support couples facing the challenges of early pregnancy loss.

Chromosomal abnormalities. The majority of early pregnancy losses are associated with chromosomal abnormalities in the conceptus. These can be numerical or structural:

- Numerical abnormalities (Aneuploidies): These involve an abnormal number of chromosomes, such as trisomy (an extra chromosome), monosomy (a missing chromosome), or polyploidy. Trisomies of chromosomes 16, 21, 22, and 15 are commonly observed in miscarriages. Monosomy X (Turner syndrome) is also frequently detected in EPL cases.
- Structural abnormalities: These include balanced or unbalanced translocations, inversions, deletions, or duplications in chromosomes. Parental balanced translocations, which do not affect the phenotype of the parent, can lead to unbalanced chromosomal complements in the fetus and result in miscarriage.

While chromosomal abnormalities are the most common genetic cause, mutations in single genes affecting embryonic development or placental function may also contribute to EPL, though these are less frequently diagnosed. Examples include:

- Mutations affecting coagulation pathways, which may increase the risk of thrombosis in the placenta.
- Genes involved in immune tolerance and implantation.

Certain maternal genetic factors can predispose to early pregnancy loss, such as thrombophilia-related gene mutations (e.g., Factor V Leiden, Prothrombin G20210A). These may contribute indirectly to pregnancy loss through placental insufficiency.

The cornerstone of genetic diagnosis in EPL is the analysis of fetal tissue obtained from the miscarriage, called products of conception (POC).

- Conventional Karyotyping: This technique involves culturing fetal cells and visualizing chromosomes under a microscope. It can detect numerical and large structural chromosomal abnormalities. However, it requires viable dividing cells, which may be difficult to obtain due to tissue degradation.
- Chromosomal Microarray Analysis (CMA): CMA is a molecular technique that can detect submicroscopic deletions or duplications (copy number variants) not visible by karyotyping. It is now increasingly used as a first-line test in miscarriage analysis due to its higher resolution and ability to detect abnormalities even in non-dividing cells.

When single-gene disorders or known maternal genetic factors are suspected, targeted genetic testing using techniques such as PCR, Sanger sequencing, or next-generation

sequencing (NGS) panels may be employed. In cases of recurrent miscarriage, parental chromosomal analysis is essential to identify balanced rearrangements or other chromosomal abnormalities that may be inherited and increase miscarriage risk.

Identifying a genetic cause of early pregnancy loss provides critical information for prognosis and future pregnancy management. For example:

- Detection of a sporadic chromosomal anomaly in a miscarriage often suggests a low recurrence risk.
- Parental balanced translocations increase the risk of subsequent miscarriages or chromosomally abnormal offspring, guiding reproductive options such as preimplantation genetic diagnosis (PGD).
- Identification of maternal thrombophilia mutations can lead to targeted interventions to reduce miscarriage risk.

Genetic counseling is an integral part of the diagnostic process, offering affected couples an understanding of the causes, recurrence risks, and available reproductive choices. Genetic abnormalities remain a predominant cause of early pregnancy loss, with chromosomal aneuploidies being the most frequent. Advances in molecular diagnostic techniques, especially chromosomal microarray analysis, have improved the detection of genetic causes in miscarriage specimens. Comprehensive genetic evaluation, combined with detailed clinical assessment, allows for better management and counseling of couples experiencing early pregnancy loss, ultimately aiding in optimizing reproductive outcomes.

Research methodology. This research adopts a comprehensive literature review methodology to synthesize current knowledge on the genetic factors and diagnostic approaches related to early pregnancy loss (EPL). Relevant studies published in peer-reviewed journals, including original research articles, reviews, and meta-analyses, were systematically identified and analyzed.

A systematic search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. Search terms combined keywords related to early pregnancy loss and genetics, such as "early pregnancy loss," "miscarriage," "chromosomal abnormalities," "genetic diagnosis," "karyotyping," and "chromosomal microarray analysis."

The search was limited to articles published in English over the last 15 years to ensure inclusion of the most recent advances in genetic diagnostic techniques. Reference lists of selected articles were also manually screened for additional relevant studies. Key data extracted from the selected articles included types of genetic abnormalities associated with EPL, diagnostic methods used (e.g., karyotyping, chromosomal microarray analysis, molecular testing), rates of detection, and clinical implications of genetic findings. The data were synthesized qualitatively to provide a comprehensive overview of the genetic

landscape of EPL and the diagnostic tools available. As this study is based on a review of published literature, no direct patient involvement or ethical approval was required. All data were handled according to ethical guidelines for research integrity and proper citation practices.

Research discussion. Early pregnancy loss (EPL) represents a significant reproductive challenge, with genetic abnormalities being the predominant etiological factor in a large proportion of cases. The discussion of genetic contributions to EPL and the effectiveness of various diagnostic tools offers insight into both the pathophysiology of miscarriage and strategies for clinical management.

Numerical chromosomal abnormalities, particularly aneuploidies such as trisomies and monosomies, are consistently reported as the most frequent genetic anomalies in miscarriage specimens. These chromosomal imbalances disrupt normal embryonic development, leading to early embryonic demise. Structural chromosomal rearrangements, although less common, also play a critical role, especially in couples with recurrent pregnancy loss (RPL), where parental balanced translocations increase the risk of unbalanced gametes.

The presence of single-gene mutations and maternal genetic predispositions adds complexity to the genetic landscape of EPL. While less frequently identified, mutations affecting coagulation, immune regulation, and implantation processes suggest that beyond chromosomal abnormalities, other genetic mechanisms may contribute to pregnancy loss. This highlights the need for broader genetic investigations, especially in unexplained or recurrent miscarriage cases.

Traditional karyotyping has long been the standard for genetic evaluation of products of conception (POC). However, its dependence on viable, dividing cells and relatively low resolution limit its diagnostic yield. Chromosomal microarray analysis (CMA) has emerged as a superior alternative, offering higher sensitivity and the ability to detect submicroscopic copy number variants and mosaicism without the need for cell culture. The increased diagnostic yield of CMA in EPL specimens supports its growing adoption in clinical practice. Moreover, molecular genetic testing, including next-generation sequencing (NGS), expands the potential to identify single-gene disorders and subtle genetic variants that may not be detectable by cytogenetic methods. These technologies, although currently more common in research or specialized settings, promise to enhance understanding of the genetic causes of EPL in the future.

Identifying genetic abnormalities in miscarriage tissue has profound implications for patient counseling and management. A sporadic chromosomal abnormality often indicates a low risk of recurrence, providing reassurance to patients. Conversely, detection of parental chromosomal rearrangements or inherited mutations necessitates targeted counseling, risk assessment for future pregnancies, and consideration of assisted

reproductive technologies such as preimplantation genetic diagnosis (PGD). Furthermore, the detection of maternal genetic factors associated with thrombophilia or immune dysfunction informs potential therapeutic interventions aimed at improving pregnancy outcomes. Integrating genetic diagnosis with comprehensive clinical evaluation facilitates personalized management plans tailored to individual patient risk profiles.

Despite advances, challenges remain in fully elucidating the genetic basis of EPL. A notable proportion of miscarriage cases remain unexplained after current genetic testing, underscoring the need for ongoing research into novel genetic causes and improved diagnostic tools. Integration of multi-omics approaches and larger cohort studies may reveal additional genetic contributors and mechanisms underlying EPL. Additionally, ethical considerations related to genetic testing, including patient consent, privacy, and psychological impact, require careful attention in clinical practice.

Conclusion. Genetic abnormalities are a predominant cause of early pregnancy loss, with chromosomal aneuploidies and structural rearrangements accounting for the majority of cases. Advances in genetic diagnostic techniques, particularly chromosomal microarray analysis and molecular genetic testing, have significantly improved the detection and characterization of these abnormalities. Accurate identification of genetic causes not only enhances understanding of the pathophysiology of miscarriage but also plays a vital role in clinical decision-making and genetic counseling. Continued research and integration of emerging technologies are essential to uncover the remaining unexplained cases and to develop personalized strategies for prevention and management. Ultimately, a comprehensive genetic evaluation of early pregnancy loss provides valuable insights that can help affected couples achieve successful pregnancies in the future.

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