

**EARLY-TERM MISCARRIAGE: GENETIC FACTORS AND MODERN
DIAGNOSTIC METHODS**

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Annotation: Early-term miscarriage, occurring within the first 12 weeks of pregnancy, remains a significant reproductive health concern, with genetic abnormalities being the predominant cause. This article reviews the key genetic factors contributing to early pregnancy loss, including chromosomal aneuploidies, structural abnormalities, and single-gene mutations. It further examines modern diagnostic methods such as karyotyping, chromosomal microarray analysis, and next-generation sequencing that have enhanced the detection and understanding of these genetic causes. Advances in genetic testing provide critical insights for clinical management, enabling personalized reproductive counseling and improved outcomes for affected couples.

Keywords: early-term miscarriage, spontaneous abortion, genetic factors, chromosomal abnormalities, aneuploidy, structural chromosomal abnormalities, genetic diagnosis, karyotyping, recurrent pregnancy loss.

Introduction. Early-term miscarriage, also known as spontaneous abortion, refers to the loss of a pregnancy within the first 12 weeks of gestation. It is a common reproductive challenge, affecting an estimated 10 to 20 percent of clinically recognized pregnancies worldwide. While miscarriage can result from a variety of causes—including maternal health conditions, environmental factors, and anatomical abnormalities—genetic factors are considered the leading cause, especially in early pregnancy loss. The earliest stages of pregnancy are a critical period of rapid cellular division and differentiation. Even minor genetic errors during this phase can lead to developmental failure, preventing the embryo from progressing to a viable fetus. Chromosomal abnormalities, including numerical and structural defects, account for nearly half of early miscarriages, highlighting the importance of genetic integrity in early embryonic development.

Despite the high prevalence of miscarriage, many couples face uncertainty about why it occurred. Historically, diagnosing the underlying cause was limited by the availability and accuracy of genetic testing methods. However, recent advances in molecular genetics and cytogenetics have dramatically enhanced our ability to detect and characterize genetic abnormalities associated with miscarriage. These technological developments not only improve diagnostic precision but also open pathways for tailored reproductive counseling and treatment. In this article, we explore the role of genetic factors in early-term miscarriage and review the state-of-the-art diagnostic methods that are reshaping clinical practice. Understanding these dimensions is essential for clinicians and patients alike, as it offers clarity, supports emotional coping, and guides future reproductive planning.

Materials and methods. This article is a comprehensive literature review aimed at summarizing current knowledge on genetic factors contributing to early-term miscarriage and the modern diagnostic techniques utilized in clinical practice.

Reviews, meta-analyses, clinical trials, cohort studies, and case series were considered. Articles not available in English or lacking sufficient methodological detail were excluded. Relevant data on types of genetic abnormalities, diagnostic methodologies, and their clinical applications were extracted and synthesized qualitatively. Particular attention was given to the sensitivity, specificity, advantages, and limitations of each diagnostic technique.

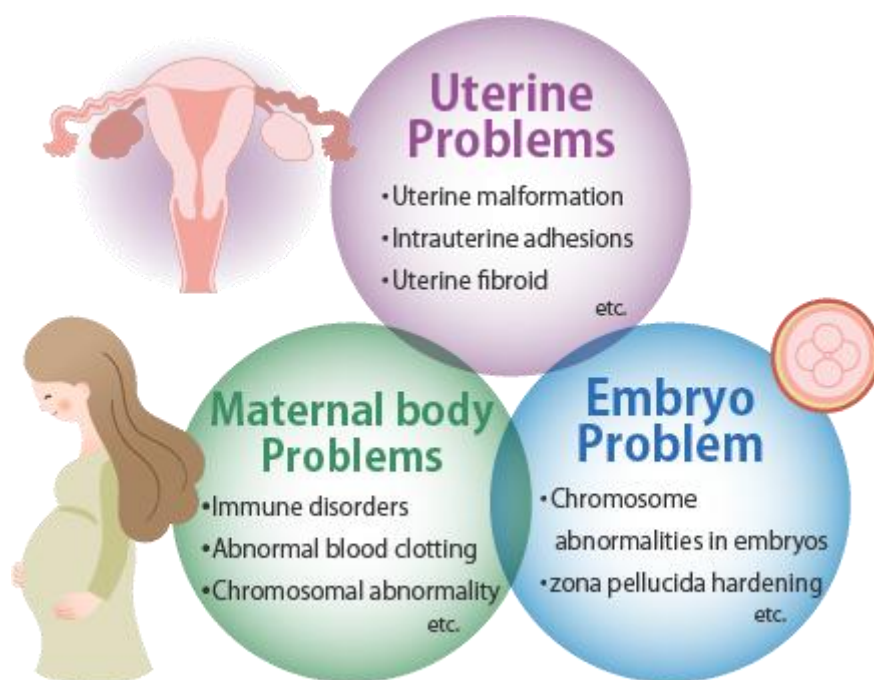


Figure 1. Recurrent miscarriage & repeated implantation failure

The majority of early miscarriages are attributed to chromosomal abnormalities in the embryo. These genetic defects often arise due to errors during the formation of eggs or sperm or during the early divisions of the fertilized egg. Common genetic causes include:

- **Aneuploidy:** The presence of an abnormal number of chromosomes, such as trisomy (extra chromosome) or monosomy (missing chromosome). Trisomy 16 and monosomy X are among the most frequent abnormalities seen in miscarried embryos.
- **Structural Chromosomal Abnormalities:** These include deletions, duplications, inversions, or translocations of chromosome segments, which can disrupt vital genetic information necessary for development.
- **Single-Gene Mutations:** Though less common, mutations in specific genes critical for embryonic development can also contribute to miscarriage.
- **Parental Genetic Factors:** Balanced chromosomal rearrangements in one of the parents can predispose embryos to unbalanced chromosomal complements, leading to miscarriage.

Table 1. Comparison of modern diagnostic methods for genetic analysis in early-term miscarriage

Diagnostic Method	Type of Genetic Abnormalities Detected	Sample Requirements	Resolution	Advantages	Turnaround Time
Karyotyping	Numerical and large structural chromosomal changes	Viable dividing cells from miscarriage tissue	Low (5–10 Mb)	Widely available; detects balanced/unbalanced abnormalities	1–2 weeks
Fluorescence In Situ	Targeted detection of specific	Fixed cells or interphase	Moderate (specific	Rapid results; detects specific	1–3 days

Diagnostic Method	Type of Genetic Abnormalities Detected	Sample Requirements	Resolution	Advantages	Turnaround Time
Hybridization (FISH)	chromosomal abnormalities	nuclei	probes)	known abnormalities	
Chromosomal Microarray Analysis (CMA)	Genome-wide copy number variations (deletions/duplications)	DNA from miscarriage tissue or blood	High (10–100 kb)	High resolution; no need for cell culture; detects submicroscopic changes	1–2 weeks
Next-Generation Sequencing (NGS)	Genome-wide detection of chromosomal abnormalities and single-gene mutations	DNA from tissue or blood	Very high (single base-pair level)	Comprehensive analysis; detects point mutations and structural variants	2–4 weeks
Preimplantation Genetic Testing (PGT)	Chromosomal abnormalities and specific genetic mutations in embryos	Embryo biopsy during IVF	High (depends on technology)	Enables selection of genetically normal embryos; reduces miscarriage risk	1–2 weeks

Understanding these genetic contributors is crucial because it informs both prognosis and potential interventions, such as preimplantation genetic diagnosis (PGD) during assisted reproductive treatments. Continued progress in genetic technologies promises to further enhance diagnosis and treatment. Integrating genetic testing with clinical factors such as maternal age, immunologic status, and uterine environment will enable personalized care strategies. Moreover, emerging methods like non-invasive prenatal testing (NIPT) and artificial intelligence-driven data analysis could offer earlier and more precise insights into pregnancy viability. Early-term miscarriage is often a complex condition with genetic abnormalities at its core. Modern diagnostic methods have vastly improved the ability to detect and understand these genetic factors, empowering healthcare providers and patients alike. By harnessing these tools, the journey from diagnosis to intervention can become more informed, hopeful, and ultimately more successful in achieving healthy pregnancies.

Research discussion. The genetic etiology of early-term miscarriage is well established, with chromosomal abnormalities representing the most frequent underlying cause. This review highlights that approximately 50% of first-trimester miscarriages result from chromosomal aneuploidies, including trisomy and monosomies, which disrupt normal embryonic development. Structural abnormalities and single-gene mutations also contribute but to a lesser extent. Understanding these genetic factors is critical because it not only clarifies the pathogenesis of pregnancy loss but also informs clinical decision-making and counseling. Modern diagnostic methods have substantially enhanced the detection and characterization of genetic abnormalities in miscarriage tissue and parental samples. Traditional karyotyping, once the gold standard, remains useful for detecting large-scale chromosomal changes and balanced rearrangements. However, its reliance on viable dividing cells and relatively low resolution limits its diagnostic yield. The advent of chromosomal microarray analysis (CMA) marked a significant improvement, allowing

detection of submicroscopic copy number variations (CNVs) that karyotyping might miss. CMA's high resolution and ability to analyze DNA directly from tissue samples make it a preferred method in many clinical settings.

Next-generation sequencing (NGS) represents the frontier of genetic diagnostics, offering comprehensive genomic insights beyond copy number changes. NGS can detect single-nucleotide variants, small insertions/deletions, and complex structural rearrangements with unprecedented precision. Its application to early miscarriage samples is growing, especially in cases of recurrent pregnancy loss where single-gene disorders or rare chromosomal abnormalities may be implicated.

Despite these technological advances, challenges remain. Variants of uncertain significance (VUS) detected by high-resolution methods complicate interpretation and counseling, sometimes causing anxiety for patients without clear clinical guidance. Moreover, balanced chromosomal abnormalities, which do not alter copy number, may be missed by CMA and require complementary techniques like karyotyping or targeted FISH. Preimplantation genetic testing (PGT) offers a proactive approach by enabling the selection of chromosomally normal embryos during assisted reproduction. While this technique reduces the risk of miscarriage due to genetic causes, it is limited to couples undergoing IVF and involves ethical, financial, and technical considerations. The integration of genetic findings with clinical data—such as maternal age, history of miscarriage, and uterine factors—is essential to formulate personalized management plans. Multidisciplinary collaboration between geneticists, reproductive specialists, and counselors ensures that patients receive comprehensive care.

Results. A substantial body of research confirms that chromosomal abnormalities are the predominant genetic cause of early-term miscarriage. Studies report that approximately 50% of miscarried embryos exhibit chromosomal aneuploidies, with trisomy 16, trisomy 22, and monosomy X among the most common abnormalities detected. Structural chromosomal abnormalities, such as translocations and inversions, are identified less frequently but are significant contributors, especially in cases of recurrent pregnancy loss. Recent genomic studies have also uncovered the role of single-gene mutations in specific genes critical for early embryonic development, although these are rarer.

Diagnostic Methods: Performance and utility:

- Karyotyping remains widely used, with diagnostic yields ranging from 40% to 60% when viable tissue is available. However, it is limited by the need for cultured dividing cells and may fail in up to 30% of samples due to tissue degradation or contamination.
- Chromosomal Microarray Analysis (CMA) shows a higher detection rate of approximately 60-70% in miscarriage specimens, owing to its ability to identify submicroscopic copy number variations undetectable by karyotyping. CMA does not require cell culture, which reduces failure rates.
- Next-Generation Sequencing (NGS), though less commonly employed in routine miscarriage analysis, has demonstrated promise in identifying both chromosomal abnormalities and single-gene mutations. Early studies report detection rates of clinically relevant variants in up to 75% of cases with recurrent pregnancy loss.
- Fluorescence In Situ Hybridization (FISH) provides rapid detection of common aneuploidies but is generally reserved for targeted analysis rather than broad screening due to its limited scope.
- Preimplantation Genetic Testing (PGT) in IVF cycles has been associated with reduced miscarriage rates by enabling the transfer of chromosomally normal embryos.

Clinical outcomes indicate improved pregnancy success rates in couples with a history of genetic-related pregnancy loss.

Recent advances integrating NGS with bioinformatics tools are facilitating the detection of complex genetic abnormalities and improving variant interpretation. Non-invasive methods, such as cell-free DNA analysis, are under investigation for earlier and less invasive diagnosis of miscarriage risk, although their clinical utility remains to be fully established.

Conclusion. Early-term miscarriage is a common and emotionally challenging event, with genetic abnormalities accounting for a significant proportion of cases. Advances in diagnostic technologies—including chromosomal microarray analysis and next-generation sequencing—have markedly improved the detection and understanding of these genetic factors. These modern methods provide higher resolution, greater accuracy, and faster results compared to traditional techniques like karyotyping. Incorporating comprehensive genetic testing into clinical practice enables more precise diagnosis, informs personalized reproductive counseling, and guides management strategies for couples experiencing pregnancy loss. Continued research and technological innovation hold promise for further reducing the incidence of miscarriage and improving outcomes through early and accurate genetic assessment.

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