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Genomic imprinting disorders and recurrent pregnancy loss

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Abstract
Genomic imprinting disorders represent a unique group of genetic conditions where the expression of certain genes is determined by the parent of origin. These disorders can significantly impact pregnancy outcomes, including recurrent pregnancy loss (RPL). This review aims to explore the relationship between genomic imprinting disorders and RPL, elucidating the underlying mechanisms, diagnostic approaches, and potential therapeutic strategies.

Keywords: Hemophagocytic syndrome (HPS), genomic imprinting disorders, recurrent pregnancy loss (RPL)

Introduction
Recurrent pregnancy loss (RPL) is a distressing condition affecting approximately 1-2% of couples attempting to conceive. Defined as the occurrence of three or more consecutive pregnancy losses before the 20th week of gestation, RPL has a multifactorial etiology encompassing genetic, anatomical, hormonal, immunological, and environmental factors. Despite extensive evaluation, the underlying cause remains unidentified in up to 50% of cases. Among the recognized genetic causes, genomic imprinting disorders have emerged as significant contributors to adverse pregnancy outcomes, including RPL. Genomic imprinting is an epigenetic phenomenon in which certain genes are expressed in a parent-of-origin-specific manner. This means that only one allele of a gene (either maternal or paternal) is active, while the other allele is silenced. The regulation of this monoallelic expression is controlled by differential DNA methylation at specific genomic regions known as imprinting control regions (ICRs). Disruptions in the normal imprinting process can lead to various imprinting disorders, which can significantly impact fetal development and viability. The mechanisms underlying genomic imprinting disorders include uniparental disomy (UPD), where an individual inherits both copies of a chromosome from one parent and none from the other; abnormal DNA methylation patterns at ICRs, which can alter gene expression; and mutations or deletions in imprinted genes, leading to functional deficiencies. These disruptions can result in either the loss of expression of essential genes or the inappropriate expression of normally silent genes, both of which can cause significant developmental abnormalities. Several well-characterized genomic imprinting disorders are associated with adverse pregnancy outcomes and have been implicated in RPL. Beckwith-Wiedemann Syndrome (BWS), Silver-Russell Syndrome (SRS), Prader-Willi Syndrome (PWS), and Angelman Syndrome (AS) are among the most notable. BWS is associated with overgrowth and an increased risk of embryonal tumors, often resulting from alterations in the imprinting of genes on chromosome 11p15. SRS is characterized by intrauterine growth restriction and postnatal growth failure, typically due to hypomethylation of the paternal imprinting control region on chromosome 11p15 or maternal UPD of chromosome 7. PWS and AS, both involving the 15q11-q13 region, result from the loss of paternal and maternal gene expression, respectively, leading to distinct clinical syndromes that can also impact pregnancy viability. Understanding the role of genomic imprinting disorders in RPL is crucial for improving diagnostic accuracy and developing targeted management strategies. The diagnosis of these disorders requires a combination of clinical evaluation, genetic testing, and molecular analysis.

Advanced diagnostic tools such as karyotyping, methylation-specific PCR, comparative genomic hybridization (CGH), and next-generation sequencing (NGS) have become indispensable in identifying imprinting abnormalities. Management of RPL associated with genomic imprinting disorders involves a multidisciplinary approach, including genetic counseling, prenatal diagnostic techniques, and tailored therapeutic interventions. For example, assisted reproductive technologies (ART) such as *in vitro* fertilization (IVF) with preimplantation genetic diagnosis (PGD) can help select embryos without imprinting defects, potentially improving pregnancy outcomes for affected couples.

Main Objective

The main objective of the study is to investigate the role of genomic imprinting disorders in contributing to recurrent pregnancy loss (RPL), with the aim of improving diagnosis, understanding pathophysiological mechanisms, and developing effective management and therapeutic strategies to enhance pregnancy outcomes for affected couples.

Pathophysiology of Genomic Imprinting Disorders

The pathophysiology of genomic imprinting disorders involves the disruption of the normal process of genomic imprinting, an epigenetic mechanism that leads to the monoallelic expression of certain genes depending on their parent of origin. This means that, for specific genes, only one allele (either maternal or paternal) is actively expressed while the other is silenced. This selective expression is regulated by differential DNA methylation patterns established during gametogenesis, which are maintained throughout the individual's life. Genomic imprinting is crucial for normal development, particularly in regulating growth, development, and metabolism. When imprinting is disrupted, it can lead to the abnormal expression of imprinted genes, resulting in various imprinting disorders. These disruptions can occur due to several mechanisms, including uniparental disomy (UPD), where an individual inherits two copies of a chromosome from one parent and none from the other; mutations or deletions in imprinted genes; and errors in the establishment or maintenance of DNA methylation at imprinting control regions (ICRs). In conditions like Beckwith-Wiedemann Syndrome (BWS), abnormalities in the imprinting of genes on chromosome 11p15, particularly involving the IGF2 and H19 genes, lead to overgrowth and an increased risk of embryonal tumors. This results from either the loss of maternal imprinting or the gain of paternal imprinting, causing both copies of IGF2 (a growth-promoting gene) to be active and both copies of H19 (a growth-suppressing gene) to be inactive. These imbalances promote excessive cell proliferation and growth. Silver-Russell Syndrome (SRS) is another example, often resulting from hypomethylation of the paternal imprinting control region on chromosome 11p15 or maternal uniparental disomy of chromosome 7. This hypomethylation leads to reduced expression of IGF2 and increased expression of H19, causing intrauterine growth restriction (IUGR) and failure to thrive postnatally. The disrupted balance between growth-promoting and growth-inhibiting genes severely impacts fetal development and viability. Prader-Willi Syndrome (PWS) and Angelman Syndrome (AS) are imprinting disorders involving the 15q11-q13 region. PWS is caused by the loss of paternal genes in this region, leading to symptoms such as hypotonia, hyperphagia, and intellectual disability. This loss can result from a deletion of the paternal chromosome 15q11-q13, maternal uniparental disomy, or defects in the imprinting center. Conversely, AS is due to the loss of maternal genes in the same region, causing severe intellectual disability, ataxia, and unique behavioral features. AS can result from a deletion of the maternal chromosome 15q11-q13, paternal uniparental disomy, or mutations in the UBE3A gene. The disruption of normal imprinting patterns in these disorders can lead to severe consequences for fetal development and pregnancy outcomes. In the context of recurrent pregnancy loss (RPL), imprinting disorders can cause early embryonic demise, intrauterine growth restriction, and other complications that lead to pregnancy failure. The exact mechanisms by which these disorders contribute to RPL are complex and involve the interplay of disrupted gene expression, impaired cellular function, and abnormal developmental processes. Overall, the pathophysiology of genomic imprinting disorders underscores the importance of tightly regulated gene expression for normal development and the profound impact that epigenetic dysregulation can have on pregnancy and fetal health. Understanding these mechanisms is critical for diagnosing and managing conditions associated with imprinting disorders and improving outcomes for affected individuals.

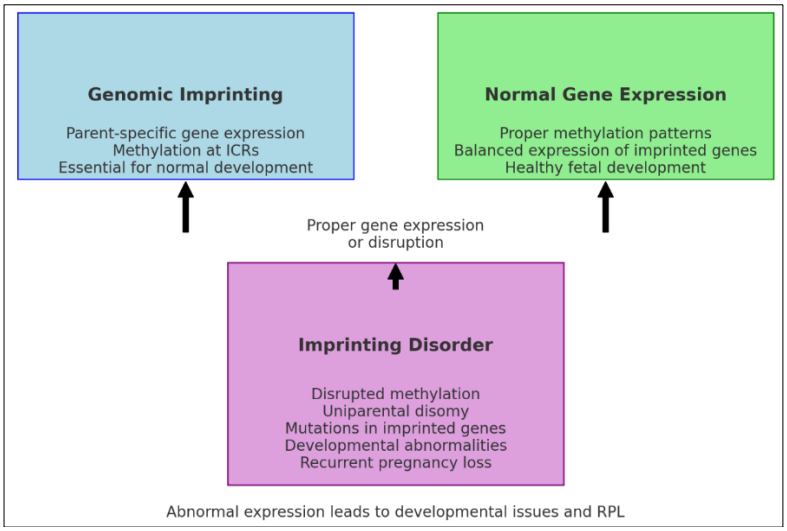

Fig 1: Genomic Imprinting Disorders

Genomic Imprinting Disorders Associated with Recurrent Pregnancy Loss

Genomic imprinting disorders are a subset of genetic conditions where the expression of certain genes is determined by their parent of origin. These disorders can significantly impact pregnancy outcomes, including causing recurrent pregnancy loss (RPL). The mechanisms underlying these disorders typically involve abnormal methylation patterns, uniparental disomy (UPD), and mutations or deletions in imprinted genes, leading to the disruption of critical developmental pathways.

Beckwith-Wiedemann Syndrome (BWS)

Beckwith-Wiedemann Syndrome (BWS) is characterized by overgrowth, macroglossia, omphalocele, and an increased risk of embryonal tumors. The disorder results from alterations in the imprinting of genes on chromosome 11p15, particularly the IGF2 and H19 genes. In BWS, there can be loss of maternal imprinting or gain of paternal imprinting, leading to the biallelic expression of IGF2 (a growth-promoting gene) and the silencing of H19 (a growth-suppressing gene). This imbalance results in excessive cell proliferation and growth, contributing to pregnancy complications and increased risk of RPL due to abnormal fetal development.

Silver-Russell Syndrome (SRS)

Silver-Russell Syndrome (SRS) presents with intrauterine growth restriction (IUGR), a triangular facial appearance, and feeding difficulties. It often results from hypomethylation of the paternal imprinting control region on chromosome 11p15 or maternal uniparental disomy of chromosome 7. Hypomethylation leads to reduced expression of IGF2 and increased expression of H19, causing severe growth restriction and developmental issues. This disrupted balance between growth-promoting and growth-inhibiting genes significantly impacts fetal viability, increasing the risk of RPL.

Prader-Willi Syndrome (PWS)

Prader-Willi Syndrome (PWS) is associated with hypotonia, hyperphagia, obesity, and intellectual disability. PWS results from the loss of paternal genes in the 15q11-q13 region due to a deletion, maternal uniparental disomy, or imprinting center defects. The loss of these paternal genes leads to a lack of critical regulatory functions necessary for normal development, which can result in early embryonic loss and contribute to RPL.

Angelman Syndrome (AS)

Angelman Syndrome (AS) is characterized by severe intellectual disability, ataxia, and unique behavioral features such as a happy demeanor and frequent laughter. AS is caused by the loss of maternal genes in the 15q11-q13 region, typically due to a deletion, paternal uniparental disomy, or mutations in the UBE3A gene. The absence of maternal gene expression disrupts neural development and function, which can cause early pregnancy failure and contribute to RPL.

Table 1: Mechanisms of Genomic Imprinting Disorders

Disorder	Mechanism	Chromosomal Region	Affected Genes
BWS	Loss of maternal imprinting or gain of paternal imprinting	11p15	IGF2, H19
SRS	Hypomethylation of paternal ICR or maternal UPD	11p15, Chromosome 7	IGF2, H19
PWS	Deletion, maternal UPD, imprinting center defects	15q11-q13	Multiple paternal genes
AS	Deletion, paternal UPD, mutations	15q11-q13	UBE3A

Conclusion

In conclusion, genomic imprinting disorders are a significant yet underrecognized cause of recurrent pregnancy loss (RPL). These disorders, characterized by parent-of-origin-specific gene expression, disrupt normal fetal development through mechanisms such as uniparental disomy, abnormal methylation patterns, and mutations in imprinted genes. Conditions such as Beckwith-Wiedemann Syndrome, Silver-Russell Syndrome, Prader-Willi Syndrome, and Angelman Syndrome exemplify the profound impact of imprinting errors on pregnancy viability. Understanding the pathophysiology of these disorders enhances our ability to diagnose and manage RPL. Diagnostic techniques, including karyotyping, methylation-specific PCR, and next-generation sequencing, are essential tools in identifying imprinting disorders. Genetic counseling and tailored therapeutic approaches, such as hormone therapy or assisted reproductive technologies with preimplantation genetic diagnosis, offer potential avenues for improving pregnancy outcomes.

Future research should focus on elucidating the full spectrum of imprinting disorders and their specific roles in RPL. This will aid in developing evidence-based guidelines and innovative therapeutic strategies, ultimately improving the prognosis for affected couples. Increased clinical awareness and multidisciplinary collaboration are crucial in addressing the complex challenges posed by genomic imprinting disorders in the context of recurrent pregnancy loss.

Conflict of Interest

Not available

Financial Support

Not available

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