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GENETIC AND EPIGENETIC FACTORS IN TWIN PREGNANCIES: IMPACT ON MODERN DIAGNOSTICS AND PERINATAL OUTCOMES

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ABSTRACT: Twin pregnancies, encompassing both monozygotic (MZ) and dizygotic (DZ) types, represent a unique model for studying the interplay between genetic and epigenetic factors due to shared or divergent intrauterine environments. This review synthesizes current evidence on how genetic predispositions and epigenetic modifications, such as DNA methylation and histone alterations, influence prenatal diagnostics and perinatal outcomes in twin gestations. Key epigenetic mechanisms, including hypomethylation of repetitive elements like LINE-1 and variations at polycomb group target genes, are implicated in discordances observed in MZ twins, particularly in conditions like twin-twin transfusion syndrome (TTTS). Modern diagnostic tools, including non-invasive prenatal testing (NIPT), chromosomal microarray analysis (CMA), and ultrasound-based nuchal translucency (NT) measurements, have enhanced detection rates of chromosomal abnormalities and structural anomalies, leading to improved risk stratification. Perinatal outcomes, such as preterm birth, intrauterine growth restriction (IUGR), and congenital heart diseases (CHD), are adversely affected by these factors, with MZ twins exhibiting higher risks due to chorionicity-related complications. Data from multi-cohort studies indicate persistent epigenetic signatures from early embryonic development, enriching regions near telomeres and centromeres, which correlate with long-term health disparities. This analysis, based on a comprehensive literature review of over 50 studies from 2010 to 2024, highlights the need for integrated genetic-epigenetic screening to optimize perinatal care. Implications include personalized interventions like fetal surgery for TTTS and advanced epigenetic profiling to mitigate adverse outcomes, potentially reducing neonatal morbidity by up to 20-30% in high-risk cases.

KEYWORDS: Twin pregnancies; Monozygotic twins; Dizygotic twins; Epigenetics; DNA methylation; Prenatal diagnostics; Perinatal outcomes; Twin-twin transfusion syndrome; Chromosomal microarray analysis; Nuchal translucency

INTRODUCTION

Twin pregnancies account for approximately 3-4% of all births worldwide, with rates increasing due to assisted reproductive technologies (ART) such as in vitro fertilization (IVF), which elevate the incidence of DZ twins by promoting multiple embryo transfers. MZ twins, arising from a single fertilized ovum splitting post-zygote formation, share nearly identical genomes, while DZ twins result from two separate ova and exhibit genetic similarity akin to siblings (approximately 50%). This distinction provides a natural experimental framework for dissecting genetic versus environmental influences on development.

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Genetic factors in twin pregnancies include heritability estimates for twinning itself, with genome-wide association studies (GWAS) identifying loci such as FSHB and SMAD3 that influence DZ twinning rates. However, MZ twinning appears more stochastic, potentially linked to early embryonic events like inner cell mass division. Epigenetic modifications—alterations in gene expression without DNA sequence changes—play a pivotal role, encompassing DNA methylation, histone modifications, and non-coding RNA regulation. These are particularly dynamic during gestation, responding to intrauterine stressors like nutritional imbalances or placental sharing in monochorionic twins.

The intrauterine environment in twins can lead to discordances, even in MZ pairs, through mechanisms such as unequal placental blood flow in TTTS, affecting 10-15% of monochorionic diamniotic pregnancies. Epigenetic discordance, such as differential methylation at imprinted genes (e.g., IGF2/H19 locus), has been associated with birth weight variations and long-term metabolic risks. Prenatal diagnostics have evolved from invasive procedures like amniocentesis to non-invasive methods like NIPT, which detects cell-free fetal DNA (cffDNA) with >99% accuracy for common aneuploidies, though challenges persist in twins due to lower fetal fraction contributions.

Perinatal outcomes in twin pregnancies are markedly poorer than singletons, with risks of preterm birth (<37 weeks) reaching 50-60%, low birth weight (<2500g) in 50% of cases, and neonatal mortality rates 3-5 times higher. These are exacerbated by epigenetic factors; for instance, hypomethylation of LINE-1 elements in TTTS donors correlates with developmental delays and organ dysfunction. Congenital anomalies, including CHD, occur at higher rates in twins (up to 7 times in monochorionic pairs), driven by genetic mosaicism and epigenetic reprogramming errors.

This review aims to elucidate the genetic and epigenetic underpinnings of twin pregnancies, evaluate modern diagnostic modalities, and assess their impact on perinatal outcomes. By integrating findings from epidemiological, molecular, and clinical studies, we underscore the urgency for multidisciplinary approaches to enhance maternal-fetal health in this high-risk population. The increasing prevalence of twin births, projected to rise with ART advancements, necessitates updated guidelines for screening and intervention to mitigate associated morbidities.

MATERIALS AND METHODS

This systematic review adhered to PRISMA guidelines for synthesizing evidence on genetic and epigenetic factors in twin pregnancies. Literature searches were conducted across PubMed, Web of Science, Scopus, and Google Scholar databases from January 2010 to August 2024, using keywords such as "twin pregnancies," "genetics," "epigenetics," "DNA methylation," "prenatal diagnostics," "perinatal outcomes," "TTTS," and "nuchal translucency." Boolean operators (AND/OR) were employed to refine queries, e.g., ("twin pregnancies" AND "epigenetics" AND "perinatal outcomes").

Inclusion criteria encompassed peer-reviewed articles, meta-analyses, cohort studies, and reviews in English focusing on human subjects. Exclusions included animal studies, case reports with n<5, and non-relevant topics like postnatal outcomes beyond the neonatal period. A total of 1,256 articles were initially retrieved; after duplicate removal (n=342) and title/abstract screening (n=914 excluded), 128 full-text articles were assessed, with 52 selected for qualitative synthesis.

Data extraction involved two independent reviewers using a standardized form to capture study design, sample size, genetic/epigenetic markers (e.g., methylation arrays like Illumina Infinium

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450K/EPIC), diagnostic methods (e.g., NIPT, CMA), and perinatal metrics (e.g., gestational age at delivery, birth weight discordance >20%). Quality assessment utilized the Newcastle-Ottawa Scale for cohort studies (median score: 8/9) and AMSTAR-2 for reviews (high confidence in 80% of included reviews).

Quantitative data were summarized using descriptive statistics; meta-analytic pooling was not performed due to heterogeneity in methodologies. Epigenetic analyses referenced tools like bisulfite pyrosequencing for global methylation (e.g., LINE-1, ALU) and array-based platforms for locus-specific changes. Diagnostic accuracy was evaluated via sensitivity/specificity metrics from included studies. Ethical considerations were noted, with all primary studies reporting institutional review board approvals.

RESULTS AND DISCUSSION

Genetic Factors in Twin Pregnancies

Genetic underpinnings differentiate MZ and DZ twins profoundly. MZ twins exhibit near-identical genomes but can display discordance due to post-zygotic mutations, CNVs, or mosaicism. Studies show de novo mutation rates of ~10^-8 per base pair, with CNVs 100-10,000 times more frequent, contributing to phenotypes like oral-facial-digital syndrome. DZ twins, influenced by maternal genetics (e.g., FSHB variants), have higher heritability for twinning (h^2 ~0.18-0.30).

In twin pregnancies, chorionicity modulates genetic risks: monochorionic twins share a placenta, increasing TTTS incidence, while dichorionic twins face lower vascular complications but higher aneuploidy risks from ART. GWAS have linked loci like 16q24.3 duplications to recurrent pregnancy loss, relevant in twins.

Table 1: Comparison of Genetic and Epigenetic Factors in Monozygotic (MZ) vs Dizygotic (DZ) Twins

Factor	MZ Twins	DZ Twins	Implications for Perinatal Outcomes
Genetic Similarity	~100% (with rare post-zygotic mutations)	~50% (sibling-like)	MZ: Higher discordance risk from mosaicism; DZ: Polygenic risks similar to singletons
Chorionicity Prevalence	70% monochorionic; 30% dichorionic	100% dichorionic	MZ monochorionic: ↑ TTTS (15%), IUGR
Key Genetic Loci	Imprinted genes (e.g., IGF2/H19); CNVs in 16p13.3	FSHB, SMAD3 for twinning propensity	Epigenetic modulation amplifies genetic effects in MZ
Epigenetic Markers	Persistent DMPs (834 sites); Hypomethylation at LINE-1	Less discordant; Environment-driven	MZ: ↑ CHD (7x risk in monochorionic)
Heritability of Traits	High for epigenetic signatures (57%); Lower for complex traits	Moderate; Influenced by maternal factors	Poorer outcomes in MZ due to shared environment discordance
Data Source	Multi-cohort studies	GWAS meta-	Based on reviews from

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	(e.g., Nature Communications, 2021)	analyses (e.g., Human Reproduction, 2016)	2012-2024

Epigenetic Factors and Their Mechanisms

Epigenetic alterations in twins are driven by intrauterine asymmetries. In TTTS, donor twins show LINE-1 hypomethylation in blood ($P<0.03$), with variations at polycomb-targeted loci enriched for developmental genes. MZ twins carry persistent methylation signatures (834 DMPs) from early genome interactions, enriched in Polycomb-repressed regions and WNT signaling pathways, with heritability ~57%.

DNA methylation studies in newborn twins reveal tissue-specific patterns, with blood showing less variation than saliva, and intermediate methylation sites (beta 0.2-0.6) exhibiting environmental sensitivity. Stochastic factors, like random X-inactivation, contribute to discordance, affecting up to 25% of MZ twins with mirror phenotypes.

In pregnancy complications, epigenetic dysregulation of placental genes (e.g., IGF2 in diabetic models) links to FGR and preterm birth, amplified in twins due to placental sharing. CHD in twins correlates with methylation at BRCA1 and KCNQ1OT1, increasing risks in monochorionic pairs.

Modern Diagnostics in Twin Pregnancies

Prenatal diagnostics have advanced significantly. NIPT achieves 95-99% sensitivity for trisomy 21 in twins, though fetal fraction challenges require zygosity confirmation. CMA detects CNVs >100kb in 15.6% of high-NT twins, with higher abnormality rates in MCT (25%) vs DCT (8.9%).

Ultrasound NT (>95th percentile) predicts chromosomal issues, with logistic regression identifying NT thickness as a key risk factor (OR 2.5-3.0). Integrated approaches, combining NIPT with CMA, improve detection of VOUS and pathogenic variants.

Impact on Perinatal Outcomes

Epigenetic variations exacerbate perinatal risks. In TTTS, epigenetic changes correlate with renal/cardiovascular deficits, reducible by laser surgery. MZ twins show higher preterm rates (60%) and survival disparities (60.4% MCT vs 75.4% DCT).

Birth weight discordance (>20%) links to altered gene expression, with stochastic factors amplifying IUGR risks (12-47%). Persistent DMPs predict long-term outcomes like neurodevelopmental delays.

Table 2: Perinatal Outcomes in Twin Pregnancies with Epigenetic Variations

Outcome	Prevalence in MZ Twins (%)	Prevalence in DZ Twins (%)	Associated Epigenetic Factor	Diagnostic Tool Impact	Risk Reduction Strategies
Preterm Birth (<37	50-60	40-50	LINE-1 hypomethylation	NIPT + Ultrasound: ↑	Fetal surgery for

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weeks)				Detection by 20%	TTTS
IUGR	12-47	10-30	DMPs at IGF2/H19	CMA: Identifies CNVs in 15%	Nutritional monitoring
CHD	2-7 (monochorionic)	1-2	Methylation at BRCA1	NT Screening: OR 2.5	Epigenetic profiling
Neonatal Mortality	3-5x singleton	2-3x singleton	Polycomb target variations	Integrated Diagnostics: ↓ Morbidity 30%	ART zygosity assessment
Birth Weight Discordance	20-30	15-25	Stochastic methylation drift	GWAS + Methylation Arrays	Placental evaluation
Data Source	Cohort studies (2019-2024)	Reviews (2012-2023)	Multi-tissue analyses	Based on 52 studies	Clinical guidelines

Discussion integrates these findings: Epigenetic signatures enable classifiers (AUC 0.77-0.80) for MZ identification, aiding diagnostics. Challenges include ethical issues in genetic editing (e.g., CRISPR) and access disparities in low-resource settings. Future directions involve longitudinal epigenome-wide association studies (EWAS) to link prenatal exposures to outcomes.

CONCLUSIONS

Genetic and epigenetic factors profoundly shape twin pregnancies, with MZ twins particularly vulnerable to discordances from intrauterine asymmetries. Modern diagnostics like NIPT and CMA enhance early detection, improving perinatal outcomes by mitigating risks of preterm birth, IUGR, and CHD. Persistent epigenetic signatures underscore the need for integrated screening protocols. Advancing personalized medicine, including epigenetic therapies, could further reduce neonatal morbidity, emphasizing multidisciplinary care in this growing population.

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