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Review Article

Placental biomarkers in pregnancy complications

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ABSTRACT

Placental biomarkers are molecular components derived from placental tissues, including proteins, hormones, nucleic acids, and metabolites, that reflect physiological and pathological changes in placental function during pregnancy. Their ability to provide a non-invasive assessment of placental function makes them valuable for the early detection and monitoring of pregnancy complications, including preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), and preterm birth, which contribute substantially to maternal and neonatal morbidity and mortality worldwide. However, evidence on placental biomarkers remains fragmented because of differences in biomarker types, detection methods, and study designs, limiting the establishment of standardized diagnostic criteria and clinical protocols. This review synthesizes current evidence on the utility and underlying mechanisms of placental biomarkers while identifying key gaps that continue to limit their clinical application. Placental biomarkers encompass diverse biological processes, including angiogenesis, endocrine regulation, gene expression, immune modulation, and metabolic homeostasis, reflecting the complex biological pathways involved in pregnancy complications. Although advances in biomarker discovery and analytical technologies have expanded their potential clinical utility, translation into routine practice remains constrained by assay variability, population heterogeneity, maternal confounding factors, and the absence of universally accepted diagnostic thresholds.

Keywords: Placenta, Biomarkers, Pregnancy complications, Preeclampsia, Diabetes, Gestational

INTRODUCTION

Placental biomarkers, comprising proteins, hormones, nucleic acids, and metabolites derived from placental tissues, serve as important molecular indicators of placental physiology and pathology throughout pregnancy. The placenta is a vital fetomaternal organ responsible for nutrient and gas exchange, endocrine hormone synthesis, and maintenance of immune tolerance at the maternal–fetal interface. The release of placental components into the maternal circulation provides an opportunity for non-invasive assessment of placental health through maternal blood sampling and may facilitate the early detection and monitoring of pregnancy complications such as preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), and preterm birth. Among the principal protein biomarkers, the angiogenic regulators soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) are particularly relevant to placental vascular function, with an imbalance between these factors associated with endothelial dysfunction in preeclampsia. Hormonal biomarkers, including human placental lactogen (hPL) and pregnancy-associated plasma protein-A (PAPP-A), reflect processes related to maternal metabolism, insulin resistance, and fetal growth. Nucleic acid biomarkers, including circulating cell-free fetal DNA (cffDNA) and placental microRNAs (miRNAs), provide information on gene regulation and immune tolerance,

while alterations in their expression have been associated with pregnancy disorders. Similarly, metabolomic profiling can identify oxidative stress markers and other metabolites that reflect changes in placental metabolic status and their association with adverse pregnancy outcomes.[1,2]

Although these biomarker classes capture different aspects of placental biology, their clinical interpretation remains challenging because their utility depends on the consistency of detection, the characteristics of the population studied, and the influence of maternal confounding factors. Consequently, assay variability, population heterogeneity, and maternal factors remain important barriers to their standardization and implementation in clinical practice.[2,3] The potential value of placental biomarkers therefore extends beyond their individual associations with pregnancy complications and lies in their capacity to provide complementary information on the diverse biological processes underlying placental dysfunction.

The clinical utility of placental biomarkers lies in their potential to identify alterations in placental function before the onset of clinical manifestations, thereby supporting earlier detection and monitoring of complications such as preeclampsia, GDM, IUGR, and preterm birth, which contribute substantially to maternal and neonatal morbidity and mortality. Accordingly, this review synthesizes the current evidence on placental biomarkers, with emphasis on their clinical utility and underlying biological mechanisms, while identifying existing knowledge gaps and limitations that may influence their interpretation and application. The review further considers the need for standardized assays and integrated multi-marker approaches to improve predictive accuracy, support clinical decision-making, and advance personalized maternal–fetal care.

METHODS

This article was conducted as a narrative review of the current literature on placental biomarkers and their potential relevance to pregnancy complications. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and Embase to identify relevant publications addressing placental biomarkers, placental function, and pregnancy-related complications. The search was supplemented by manual examination of the reference lists of relevant articles to identify additional publications of potential relevance.

The search strategy incorporated controlled vocabulary, including Medical Subject Headings (MeSH) where applicable, together with free-text terms and combinations of keywords such as “placental biomarkers,” “placental dysfunction,” “pregnancy complications,” “preeclampsia,” “gestational diabetes mellitus,” “fetal growth restriction,” “intrauterine growth restriction,” “preterm birth,” “angiogenic biomarkers,” “microRNAs,” “cell-free fetal DNA,” “metabolomics,” and “oxidative stress.” Boolean operators (AND, OR) and truncation strategies were used to broaden or refine the search as appropriate. The literature search focused primarily on human studies published in the English language, with emphasis on recent evidence while also considering earlier seminal studies where they provided important mechanistic or conceptual foundations.

Relevant original research articles, systematic reviews, meta-analyses, narrative reviews, and other peer-reviewed publications were considered based on their relevance to the scope of this review. Studies addressing animal models, unrelated pregnancy outcomes, or biomarkers without clear relevance to placental function or pregnancy complications were generally excluded from the narrative synthesis. Reference selection was guided primarily by scientific relevance, methodological quality, recency, and contribution to understanding the biological mechanisms or clinical utility of placental biomarkers.

The literature was organized thematically according to major biomarker classes, including proteins, hormones, nucleic acids, and metabolites, followed by consideration of their roles in specific pregnancy complications and the underlying mechanisms linking biomarker alterations with placental dysfunction. Particular attention was given to angiogenesis, endocrine regulation, immune modulation, inflammation, oxidative stress, and metabolic pathways. Evidence concerning biomarker detection methods, clinical applicability, predictive potential, and limitations was also considered.

Because this was a narrative review, findings were synthesized qualitatively rather than through formal quantitative meta-analysis. Greater emphasis was placed on recent and clinically relevant evidence, while established earlier studies were retained where necessary to provide biological context. Differences in study populations, gestational age, sample type, biomarker characteristics, analytical methods, and clinical outcome definitions were considered when interpreting the available evidence. The review also identified current knowledge gaps and challenges related to biomarker standardization, reproducibility, validation, and translation into clinical practice.

RESULTS

Types of placental biomarkers

Proteins

Placental proteins provide important indicators of vascular development, trophoblast function, and overall placental integrity. Among the biomarkers described in the literature, placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and pregnancy-associated plasma protein-A (PAPP-A) are particularly relevant

because of their involvement in angiogenic regulation and trophoblast biology.

PlGF has a predominantly pro-angiogenic role and contributes to the development and maintenance of the placental vasculature, supporting adequate maternal–fetal exchange. In contrast, sFlt-1 functions as an anti-angiogenic decoy receptor by binding vascular endothelial growth factor (VEGF) and PlGF and thereby limiting their signaling. The relationship between these two biomarkers is therefore clinically relevant: increased sFlt-1 together with reduced PlGF reflects an imbalance in angiogenic signaling associated with endothelial dysfunction and impaired placental perfusion. This imbalance is particularly important in the pathophysiology of preeclampsia.[4,5]

PAPP-A represents a complementary marker of placental function. As a placental metalloprotease, it regulates insulin-like growth factor (IGF) bioavailability through cleavage of IGF-binding proteins, thereby influencing trophoblast invasion and fetal growth. Altered PAPP-A concentrations have been associated with abnormal fetal growth and adverse pregnancy outcomes, including preeclampsia and intrauterine growth restriction (IUGR). Thus, PAPP-A may provide information not only on placental status but also on pathways linking placental function with fetal growth.[6]

The clinical relevance of placental protein biomarkers is further demonstrated by the sFlt-1/PlGF ratio, which integrates the opposing angiogenic signals represented by these two markers. An increased ratio has diagnostic and prognostic relevance in preeclampsia and may indicate disease risk and severity before overt clinical manifestations. Nevertheless, its performance can differ according to the population and clinical context in which it is applied, supporting the need for interpretation alongside the overall clinical assessment. Collectively, these protein biomarkers provide complementary information on placental angiogenic activity, trophoblast-related function, and pregnancy risk, with relevance to the assessment of preeclampsia and other placental complications.[7]

Hormones

Hormonal biomarkers secreted by the syncytiotrophoblast are integral to the maintenance of pregnancy and the orchestration of maternal metabolic adaptations critical for fetal development. Principal among these is human Chorionic Gonadotropin (hCG) and hPL. hCG sustains early gestation by supporting corpus luteum viability and progesterone synthesis, which are essential for endometrial receptivity and pregnancy continuation. Beyond its luteotropic function, hCG facilitates uterine angiogenesis, promotes cytotrophoblast differentiation into syncytiotrophoblast cells, inhibits myometrial contractility, and contributes to uterine growth throughout gestation. Conversely, hPL modulates maternal glucose and lipid metabolism by inducing insulin resistance and lipolysis, thereby augmenting nutrient availability to the fetus.[8,9]

Alterations in the secretion dynamics of these hormones have been implicated in the pathogenesis of metabolic pregnancy complications. Although hPL is mechanistically linked to gestational insulin resistance, systematic reviews indicate inconsistent associations between absolute hPL concentrations and GDM diagnosis, highlighting the complexity of its role in maternal glycemic regulation. PAPP-A, a placental metalloprotease rather than a hormone, modulates IGF bioavailability through cleavage of IGF binding proteins, thereby influencing trophoblast invasion and fetal growth trajectories. Aberrant PAPP-A levels have been correlated with fetal growth abnormalities and placental insufficiency, underscoring its significance in placental development and metabolic regulation.[10]

The endocrine activity of the placenta, as reflected by these hormonal biomarkers, is essential for maternal-fetal nutrient exchange and metabolic homeostasis. Dysregulation of placental hormone secretion not only serves as a biomarker of placental dysfunction but also contributes mechanistically to the etiology of metabolic complications.[11]

Nucleic acids

Circulating cffDNA and placental miRNAs, represent critical molecular entities that reflect gene regulatory networks and immune modulation at the maternal-fetal interface. cffDNA, predominantly released into maternal circulation via apoptotic trophoblasts, offers a non-invasive biomarker for prenatal diagnostics and early detection of placental dysfunction. Quantitative and qualitative alterations in cffDNA levels have been correlated with adverse pregnancy outcomes such as preeclampsia and IUGR, underscoring its potential utility in early risk stratification.[12,13]

Placental miRNAs, a class of small non-coding RNAs, exert post-transcriptional regulation of gene expression and are integral to placental development, immune tolerance, angiogenesis, and metabolic homeostasis. Dysregulation of specific miRNA profiles has been implicated in the pathophysiology of pregnancy complications, including preeclampsia and IUGR, suggesting their role in epigenetic modulation of placental pathology. Furthermore, genetic analyses reveal that immune biomarker loci enriched within placental cell populations overlap with susceptibility loci for pregnancy disorders, highlighting the significance of nucleic acid biomarkers in orchestrating pregnancy-specific immune responses.

The temporal dynamics of these nucleic acid biomarkers throughout gestation mirror the evolving placental environment and maternal-fetal interactions. Collectively,

nucleic acid biomarkers provide mechanistic insights into gene expression patterns and immunological processes unique to gestation, enabling early identification of placental dysfunction and informing personalized clinical management of pregnancy complications.[14,15]

Metabolites

Metabolites represent a crucial class of placental biomarkers, comprising small-molecule compounds such as amino acids, lipids, and oxidative stress markers that reflect the metabolic and redox state of the placenta. Metabolomic profiling of these molecules provides a dynamic and sensitive snapshot of placental biochemical activity and cellular stress responses. Alterations in metabolite profiles have been strongly associated with pregnancy complications, particularly preterm birth and preeclampsia. Increased levels of oxidative stress metabolites, including lipid peroxidation products, signal placental hypoxia and cellular injury, which are key features in the pathophysiology of these disorders.[16,17]

Additionally, lipid dysregulation detected through metabolomic analyses further characterizes placental dysfunction and its contribution to adverse pregnancy outcomes. Environmental factors such as prenatal air pollution exposure have also been linked to changes in placental metabolites, including mitochondrial DNA content and telomere length, indicating oxidative stress and accelerated cellular ageing within placental tissues. Collectively, metabolite biomarkers complement protein, hormone, and nucleic acid markers by providing insights into the biochemical and oxidative environment of the placenta, thus enhancing understanding of placental pathology and facilitating early detection and monitoring of pregnancy complications.[18]

Collectively, these biomarker categories integrate angiogenic, endocrine, genetic, immune, metabolic, and oxidative pathways, providing a comprehensive framework for understanding placental pathophysiology and informing early diagnostic, prognostic, and therapeutic strategies.[19,20] Table 1 summarizes the placental biomarkers and their clinical significance.

Table 1: Classification of placental biomarkers and their association with pregnancy complications.

Type	Key markers	Role in complications	Associated conditions
Proteins	sFlt-1, PlGF, PAPP-A	Elevated sFlt-1 and reduced PlGF disrupt endothelial function and placental blood supply. Altered PAPP-A impairs trophoblast invasion and fetal growth.	Preeclampsia, IUGR
Hormones	hCG, hPL	hCG abnormalities signal early pregnancy failure; hPL dysregulation drives maternal insulin resistance and metabolic disruption.	GDM, placental dysfunction
Nucleic acids	cffDNA, miRNAs	Quantitative changes in cffDNA and miRNA dysregulation reflect epigenetic disruption of angiogenesis and immune tolerance at the maternal-fetal interface.	Preeclampsia, IUGR
Metabolites	Lipids, oxidative stress markers	Lipid peroxidation products indicate placental hypoxia and cellular injury; lipid dysregulation reflects placental metabolic failure.	Preeclampsia, preterm birth

Detection and analysis methods

The detection and quantification of placental biomarkers utilize advanced analytical methodologies specifically adapted to the molecular characteristics of each biomarker class, ensuring optimal sensitivity, specificity, and clinical relevance. Protein and hormonal biomarkers are primarily measured through immunoassays such as Enzyme-Linked Immunosorbent Assay (ELISA) and multiplex bead-based platforms, which provide robust, high-specificity quantification with broad dynamic ranges. These assays enable reliable detection of key angiogenic factors, including sFlt-1 and PlGF, as well as endocrine hormones like hPL, predominantly from maternal blood samples, facilitating non-invasive and longitudinal monitoring of placental vascular and endocrine function.[2,21]

cffDNA and placental miRNAs, are analyzed using sensitive molecular biology techniques such as quantitative polymerase chain reaction (qPCR), next-generation sequencing (NGS), and microarray technologies applied to maternal plasma or serum, facilitating non-invasive, longitudinal monitoring of placental health. These approaches allow precise quantification and comprehensive profiling of gene regulatory elements and immune modulators at the maternal-fetal interface, supporting dynamic assessment of placental gene expression and epigenetic modifications throughout gestation.

Metabolomic biomarkers, reflective of placental metabolic and oxidative states, are characterized via high-resolution platforms including mass spectrometry (MS) and nuclear

magnetic resonance (NMR) spectroscopy. These techniques identify and quantify small molecule metabolites, oxidative stress markers, and lipid profiles in maternal circulation, providing detailed biochemical insights into placental cellular stress and dysfunction. Collectively, these methodologies, predominantly reliant on maternal blood sampling, offer a multidimensional, non-invasive strategy for early diagnosis, prognostication, and personalized management of pregnancy complications.[16,22]

Role in specific pregnancy complications

Placental biomarkers not only reflect underlying placental dysfunction but also actively contribute to the mechanistic pathways driving disease progression, encompassing angiogenic imbalance, endocrine disruption, immune dysregulation, and oxidative stress. Their integration into clinical assessment offers valuable insights into early diagnosis, risk stratification, and personalized management of pregnancy-related adverse outcomes.[3,23]

Preeclampsia

Preeclampsia is a multifactorial gestational disorder characterized by dysregulated placental angiogenesis and systemic maternal endothelial dysfunction. This pathology is marked by elevated circulating levels of sFlt-1, an anti-angiogenic glycoprotein that sequesters VEGF and PlGF, thereby attenuating their pro-angiogenic signaling essential for placental vascular development and homeostasis. The resultant imbalance, typified by increased sFlt-1 and decreased PlGF concentrations, precipitates impaired uteroplacental perfusion and widespread endothelial injury, clinically manifesting as hypertension and multiorgan involvement. The sFlt-1/PlGF ratio has been extensively validated as a predictive and diagnostic biomarker for preeclampsia, often rising prior to overt clinical symptoms, thus enabling early risk stratification and timely therapeutic intervention. However, its diagnostic accuracy may vary according to population heterogeneity and clinical context, necessitating integration with comprehensive clinical evaluation for optimal management.[24,25]

GDM

GDM is characterized by dysregulated maternal glucose metabolism, partially attributable to placental endocrine dysfunction. hPL plays a pivotal role in promoting maternal insulin resistance and lipolysis, thereby enhancing glucose availability to the fetus, a process essential for fetal growth but which may exacerbate maternal hyperglycemia when aberrantly regulated. Despite its mechanistic involvement, systematic reviews and meta-analyses reveal inconsistent associations between absolute hPL concentrations and GDM diagnosis, indicating an incomplete understanding of its precise role in gestational glucose homeostasis. PAPP-A, modulates IGF bioavailability; altered PAPP-A levels have been correlated with fetal growth abnormalities, underscoring its significance in placental metabolic regulation and GDM pathophysiology.[26,27]

In addition to hormonal perturbations, placental microRNAs (miRNAs) implicated in metabolic regulation exhibit altered expression profiles in GDM, suggesting epigenetic mechanisms contributing to disease pathogenesis. These miRNA dysregulations affect gene expression pathways related to insulin signaling, inflammation, and placental function, further exacerbating metabolic imbalance and influencing fetal growth trajectories. Empirical evidence consistently demonstrates correlations between these biomarker alterations and both the severity of GDM and associated fetal growth abnormalities, highlighting their utility in risk stratification, early detection, and longitudinal monitoring of GDM pregnancies. The integrated assessment of endocrine and nucleic acid biomarkers thereby provides mechanistic insights into the complex metabolic disruptions underlying GDM and supports the advancement of personalized clinical management strategies.[28]

Preterm birth

Preterm birth is closely associated with placental dysfunction characterized by a complex interplay of inflammatory processes, oxidative stress, and vascular abnormalities. Elevated levels of oxidative stress biomarkers, including lipid peroxidation products, alongside pro-inflammatory cytokines derived from placental tissues, have been implicated in the pathogenesis of preterm labor by reflecting underlying placental hypoxia and cellular injury. Concurrently, dysregulation of specific placental miRNAs involved in immune regulation disrupts maternal-fetal immune homeostasis, further contributing to the etiopathogenesis of preterm delivery. Metabolomic analyses reveal distinct biochemical signatures in maternal circulation preceding preterm birth, underscoring the potential of these metabolic biomarkers as early, non-invasive diagnostic indicators. Collectively, these placental biomarkers encapsulate multifactorial mechanisms immune dysregulation, oxidative damage, and compromised vascular integrity that drive preterm birth, offering critical avenues for early risk stratification and targeted clinical intervention.[29]

Mechanisms by which biomarkers influence complications

Placental biomarkers influence pregnancy complications through multiple interconnected biological pathways

Angiogenesis

Placental biomarkers modulate pregnancy complications through multifaceted biological pathways, with angiogenesis playing a central role in placental vascular development and maternal endothelial integrity. Pro-

angiogenic factors such as PlGF and VEGF promote vascular formation and maintenance, whereas anti-angiogenic proteins like sFlt-1 act as decoy receptors that sequester VEGF and PlGF, thereby attenuating their signaling. Elevated circulating sFlt-1 disrupts angiogenic homeostasis, leading to impaired placental vascularization, diminished uteroplacental perfusion, and systemic maternal endothelial dysfunction. This angiogenic imbalance, characterized by increased sFlt-1 and decreased PlGF levels, is pathognomonic of preeclampsia and precedes clinical manifestations such as hypertension and multi-organ involvement. Consequently, these angiogenic biomarkers serve as critical early indicators of placental ischemia and vascular pathology, enabling risk stratification and facilitating timely clinical intervention.[30,31]

Endocrine regulation

The placenta functions as a critical endocrine organ orchestrating maternal metabolic adaptations essential for fetal development through the secretion of key hormonal biomarkers such as hPL and hCG. hPL facilitates maternal insulin resistance and lipolysis, thereby augmenting glucose and lipid availability to the fetus, a process vital for fetal growth yet contributory to maternal hyperglycemia when dysregulated. PAPP-A, modulates IGF bioavailability, influencing trophoblast invasion and placental development. Dysregulation of these endocrine factors underpins metabolic perturbations characteristic of GDM, marked by maternal hyperglycemia and aberrant fetal growth patterns, although the precise quantitative role of hPL in GDM pathogenesis requires further elucidation. Additionally, altered placental hormone secretion reflects disrupted endocrine homeostasis, exacerbating insulin resistance and nutrient imbalance, thereby impacting pregnancy outcomes. These endocrine biomarkers provide mechanistic insights into gestational metabolic regulation and serve as valuable markers for early detection, risk stratification, and longitudinal monitoring of GDM and related complications.[32,33]

Immune modulation and inflammation

Placental miRNAs and cytokines critically regulate immune tolerance and inflammatory pathways at the maternal-fetal interface, preserving the immunological equilibrium essential for successful gestation. Perturbations in the expression of specific placental miRNAs and pro-inflammatory cytokines disrupt this homeostasis, precipitating placental inflammation that contributes to the etiology of pregnancy complications such as preterm birth and IUGR. These aberrant immune responses initiate inflammatory cascades that exacerbate placental tissue injury, promote oxidative stress, and may trigger premature labor mechanisms. Genetic investigations further reveal that immune-related biomarker loci enriched within placental cellular subsets coincide with susceptibility regions for adverse pregnancy outcomes, underscoring the integral role of immune modulation in placental pathophysiology. Consequently, these immune biomarkers not only serve as indicators of placental dysfunction but also actively mediate pathological processes impairing placental integrity and fetal development.[34,35]

Oxidative stress

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanisms, induces cellular damage within placental tissues, manifesting as elevated levels of lipid peroxidation products that signify placental hypoxia and mitochondrial dysfunction. This oxidative insult contributes to placental insufficiency, cellular injury, and activation of inflammatory cascades, which are pathophysiologically linked to adverse gestational outcomes, including preeclampsia and preterm birth. Exogenous factors such as prenatal air pollution exacerbate oxidative stress, accelerating placental cellular senescence and functional decline. Metabolomic profiling effectively captures these biochemical perturbations, yielding dynamic biomarkers that precede clinical manifestations of placental pathology. The identification of oxidative stress markers thus facilitates early detection of at-risk pregnancies and informs the development of targeted antioxidant therapeutic strategies aimed at mitigating placental injury.[36]

Clinical implications

Placental biomarkers offer pivotal clinical utility by enabling early, non-invasive, and objective evaluation of placental function and pathology, which is essential for the timely diagnosis and management of pregnancy-related complications. The sFlt-1/PlGF ratio, a rigorously validated biomarker, facilitates early prediction and stratification of preeclampsia severity, thereby guiding tailored clinical interventions before symptom onset, although its diagnostic performance necessitates contextual interpretation within specific patient populations and alongside established clinical criteria. Endocrine markers such as hPL enhance understanding of gestational metabolic adaptations, while PAPP-A, a metalloprotease, serves as a critical indicator for fetal growth aberrations and placental insufficiency, supporting individualized monitoring. Additionally, nucleic acid and metabolomic biomarkers augment diagnostic precision by reflecting underlying gene regulatory dynamics and metabolic perturbations. The integration of multi-marker panels combined with comprehensive clinical data promises to refine predictive accuracy and facilitate personalized prenatal care, ultimately improving maternal and fetal outcomes.[7,37]

Future directions

Advancement in the clinical integration of placental biomarkers necessitates rigorous standardization, validation, and enhancement of assay accessibility to

facilitate widespread adoption. The development of cost-effective, rapid, and user-friendly diagnostic platforms is critical to enable routine implementation across diverse healthcare settings. Integration of biomarker data with comprehensive clinical parameters will augment risk stratification accuracy and support personalized prenatal management. Longitudinal biomarker profiling throughout gestation offers the potential to refine temporal risk assessment and optimize intervention timing. Achieving these objectives requires interdisciplinary collaboration among obstetricians, molecular biologists, bioinformaticians, laboratory specialists, healthcare policymakers, and industry stakeholders to accelerate biomarker discovery, validation, and translation. Such concerted efforts will underpin the establishment of standardized protocols, multiplex biomarker panels, and evidence-based clinical guidelines.[2]

Future research on placental biomarkers should prioritize large-scale, prospective validation studies involving diverse populations and independent clinical settings to improve generalizability, establish reproducibility, and reduce inter-study variability. Integrative multi-omics approaches combining proteomic, genomic, transcriptomic, and metabolomic data may provide a more comprehensive characterization of the molecular pathways underlying placental dysfunction and facilitate the identification of multimodal biomarker signatures with improved predictive performance.

The integration of molecular biomarkers with maternal characteristics, biophysical measurements, ultrasound and Doppler parameters, and longitudinal clinical data may further refine risk-prediction models and enable dynamic risk stratification across gestation. Such approaches could support personalized surveillance and clinical decision-making while facilitating the identification of novel biological pathways and potential therapeutic targets, thereby contributing to the development of precision medicine strategies for placental-related pregnancy complications.[38,39]

Challenges and limitations

The clinical translation of placental biomarkers is impeded by considerable challenges, including heterogeneity in biomarker classifications and variability in detection methodologies, which collectively hinder the establishment of standardized diagnostic thresholds and clinical guidelines. Analytical limitations such as assay sensitivity, specificity, and reproducibility are particularly pronounced for emergent biomarker classes like miRNAs and metabolites. Additionally, maternal confounders, including demographic factors, comorbid conditions, and environmental exposures, exert significant influence on biomarker expression, necessitating rigorous contextual interpretation to mitigate diagnostic inaccuracies. The multifactorial etiology of pregnancy complications further limits the predictive capacity of individual biomarkers, emphasizing the imperative for integrated multi-marker panels and composite clinical algorithms. Ethical considerations surrounding prenatal biomarker testing and result disclosure impose additional complexities, mandating structured counseling frameworks to support patient autonomy and informed decision-making.[2,40]

CONCLUSION

Placental biomarkers provide valuable insights into placental function and dysfunction, enabling the early detection and monitoring of major pregnancy complications such as preeclampsia, gestational diabetes mellitus, intrauterine growth restriction, and preterm birth. Advances in biomarker discovery and analytical technologies have enhanced their potential for non-invasive risk assessment and personalized prenatal care. Further standardization, large-scale validation, and integration of multi-marker approaches are essential to facilitate their routine clinical application and improve maternal and neonatal outcomes.

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