Review Article

Access this article online

Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_29_25

Nanoflower biosensors in the first trimester: A paradigm shift in the early detection of pregnancy complications

Wiku Andonotopo[1], Muhammad Adrianes Bachnas[2], Julian Dewantiningrum[3], Mochammad Besari Adi Pramono[4], I Nyoman Hariyasa Sanjaya[5], Milan Stanojevic[6], Asim Kurjak[7]

[1]Department of Obstetrics and Gynecology, Fetomaternal Division, Women Health Center, Eka Hospital BSD City, Tangerang, Banten, [2]Department of Obstetrics and Gynecology, Fetomaternal Division, Medical Faculty of Sebelas Maret University, Dr. Moewardi Hospital, Solo, Surakarta, [3]Department of Obstetrics and Gynecology, Fetomaternal Division, Medical Faculty of Diponegoro University, Dr. Kariadi Hospital, Semarang, [4]Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Division, Faculty of Medicine Universitas Udayana, Prof. dr. I.G.N.G Ngoerah General Hospital, Bali, Indonesia, [5]Department of Neonatology and Rare Diseases, Medical University of Warsaw, Warsaw, Poland, [6]Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia

Address for correspondence:
Dr. Wiku Andonotopo, Department of Obstetrics and Gynecology, Fetomaternal Division, Women Health Center, Eka Hospital BSD City, Serpong, Tangerang, Banten, Indonesia.
E-mail: wiku.andonotopo@gmail.com

Submitted: 09-Jul-2025
Revised: 12-Aug-2025
Accepted: 22-Aug-2025
Published: 29-Sep-2025

Abstract:

Detecting pregnancy complications during the first trimester remains a major challenge in obstetric care, as current screening tools often lack sensitivity to identify early risks such as preeclampsia, preterm birth, and gestational diabetes. Advances in nanotechnology, particularly nanoflower biosensors, have created new opportunities for precise, noninvasive diagnostics. Nanoflowers are nanoscale, flower-like structures with high surface area and unique electronic properties, enabling ultrasensitive detection of low-abundance biomarkers including placental growth factor, human chorionic gonadotropin variants, circulating cell-free DNA, and microRNAs. This review synthesizes the biological principles, fabrication techniques, and diagnostic applications of nanoflower biosensors, with emphasis on first-trimester implementation. Platforms discussed include metal–organic frameworks, carbon nanostructures, and hybrid composites, evaluated for sensitivity, signal amplification, and adaptability to point-of-care settings. Evidence from preclinical and clinical studies highlights their superior detection thresholds compared with conventional assays, supporting earlier recognition of complications and potential integration into predictive models. While the promise of nanoflower biosensors lies in advancing first-trimester surveillance, translation into clinical practice requires larger validation cohorts, regulatory alignment, and ethical safeguards to address risks of overdiagnosis and inequity. Future directions include multiplex detection, mobile health integration, and personalized risk stratification pathways. By bridging nanotechnology and maternal–fetal medicine, nanoflower biosensors represent a paradigm shift toward precision diagnostics in prenatal care, offering transformative potential for early intervention and improved maternal and neonatal outcomes.

Keywords:

First-trimester screening, nanoflower biosensors, nanotechnology, pregnancy complications, prenatal diagnostics

Introduction

Pregnancy complications such as preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction, and spontaneous preterm birth continue to represent significant contributors to maternal and neonatal morbidity worldwide.[1-3] Despite advancements in obstetric care, the ability to predict these outcomes during the first trimester remains limited, with most clinical tools detecting pathophysiological changes only after symptoms or structural abnormalities emerge.[4,5] This diagnostic delay often precludes early interventions that could meaningfully alter maternal–fetal outcomes.[6]

Current screening protocols, such as the combined first-trimester test, maternal serum markers, and uterine artery Doppler

How to cite this article: Andonotopo W, Bachnas MA, Dewantiningrum J, Pramono MB, Sanjaya IN, Stanojevic M, *et al*. Nanoflower biosensors in the first trimester: A paradigm shift in the early detection of pregnancy complications. Philipp J Obstet Gynecol 2025;49:149-60.

velocimetry, provide modest predictive value and are constrained by biological variability, assay limitations, and low specificity for certain complications.[7-9] Furthermore, most biomarker discovery efforts remain focused on the second or third trimester, thus failing to exploit the early window of gestation when placental and endothelial dysfunction begins to evolve.[10,11]

Nanotechnology, particularly in the form of nanoflower biosensors, offers a transformative platform for biomolecular detection.[12-15] These three-dimensional, hierarchical nanostructures – characterized by high surface-to-volume ratios and tunable electrochemical properties – enable ultrasensitive detection of low-abundance biomarkers in blood, urine, or cervical secretions.[16,17] Unlike traditional assays, nanoflower biosensors can be functionalized to simultaneously detect multiple analytes, offering a multiplexed and potentially point-of-care approach for early risk stratification.[18,19]

To date, no comprehensive review has synthesized the state-of-the-art in nanoflower biosensors applied specifically to first-trimester detection of pregnancy complications.[20] This review addresses that gap by critically analyzing the mechanisms, clinical studies, and translational potential of nanoflower biosensors in early gestation.

The aim of this review is to map and evaluate the current landscape of nanoflower biosensor technologies within a perinatal framework, define their potential integration into clinical pathways, and articulate both the promises and ethical challenges inherent in predicting obstetric complications at such an early stage. In doing so, this work provides a foundation for interdisciplinary innovation between nanotechnology, obstetrics, and maternal–fetal medicine. Figure 1 illustrates the literature screening and selection process conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and forms the methodological foundation for this review.

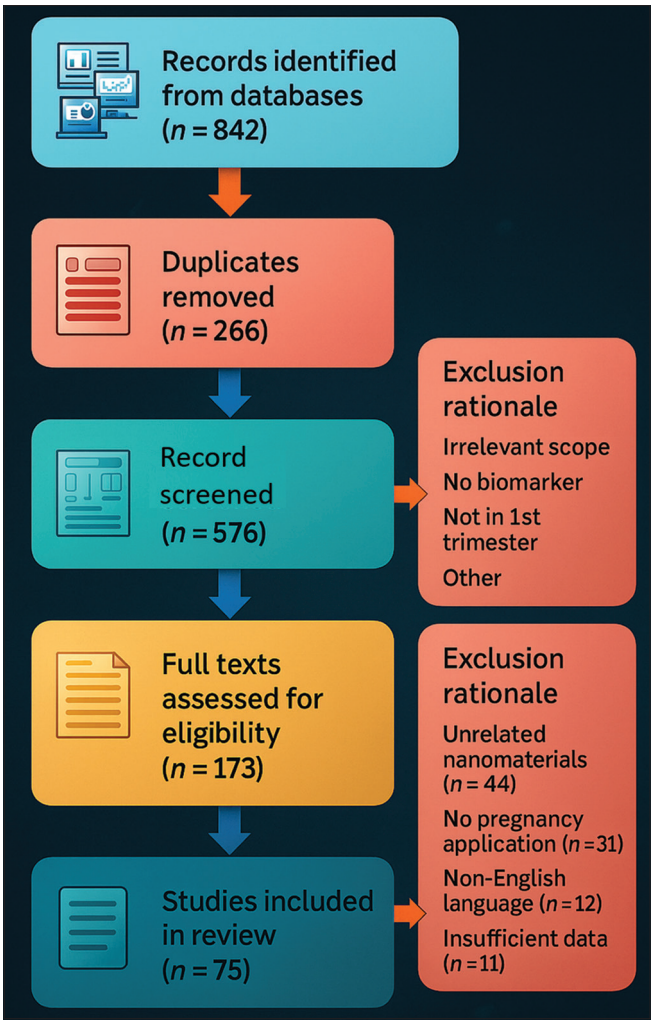

Figure 1: Literature Screening and Selection Process Based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines. This PRISMA 2020 flow diagram outlines the systematic review process for studies on nanoflower biosensors in early pregnancy. A total of 842 records were identified through major databases. After removing 266 duplicates, 576 articles underwent title and abstract screening, of which 403 were excluded for irrelevance, lack of biomarkers, or being outside the first-trimester scope. The remaining 173 full-text articles were assessed, and 98 were excluded due to use of unrelated nanomaterials (n = 44), nonpregnancy-specific focus (n = 31), non-English language (n = 12), or insufficient methodological details (n = 11). Ultimately, 75 high-quality studies were included in the final synthesis

Methodology

This review was conducted following the PRISMA 2020 guidelines, ensuring methodological transparency and replicability. Although the protocol was not preregistered, all major stages of systematic review – identification, screening, eligibility, and inclusion – were meticulously followed.

A comprehensive literature search was carried out using PubMed, Scopus, and Web of Science databases, targeting publications from January 2000 to June 2025. The search strategy incorporated combinations of controlled vocabulary (MeSH) and free-text terms such as "nanoflower," "3D nanostructures," "hierarchical nanomaterials," "biosensor," "nanosensor," "nanoparticle," "microRNA assays," "biomarker/glucose detection," "electrochemical sensor," "microRNA sensors," "electrochemical platforms," "pregnancy complications," "gestational diabetes," "preeclampsia," "preterm birth," "first trimester," "early pregnancy," and "prenatal screening."[21-23] In addition to database queries, reference lists of included studies and relevant reviews were hand-searched to identify additional eligible articles.

Studies were considered for inclusion if they described the development, functional characterization, or clinical

application of nanoflower biosensors aimed at detecting biomarkers related to pregnancy complications. Eligible studies included both preclinical and clinical investigations, provided they addressed the utility of nanoflower biosensors within the context of early pregnancy or first-trimester screening. Only original research published in English was included. Studies focusing on non-nanoflower-based sensors, unrelated pathologies, or lacking primary data were excluded. Review articles, editorials, and conference abstracts without sufficient methodological details were also excluded.[24-26]

The initial screening of titles and abstracts was independently performed by two reviewers. Full-text screening was conducted for all articles deemed potentially relevant. Discrepancies between reviewers were resolved through consensus, with a third reviewer consulted in cases of disagreement. The final list of included studies underwent rigorous quality assessment.

To ensure objective evaluation of methodological robustness, multiple validated appraisal tools were applied. The AMSTAR-2 instrument was used to assess the methodological quality of any included reviews.[27] The Newcastle–Ottawa Scale (NOS) was applied to observational, cohort, or case–control studies,[28] while the ROBIS tool was employed to evaluate risk of bias in any existing systematic evidence.[29] Studies were assigned qualitative ratings of high, moderate, or low methodological quality based on these instruments.

Data from the selected studies were extracted using a structured template designed to capture essential variables. This included the type of nanoflower biosensor and its material composition, fabrication technique, biomarker specificity, biological matrix tested (e.g., serum, urine, saliva, and cervical fluid), method of detection (electrochemical, optical, fluorescence-based, etc.), gestational age at detection, diagnostic performance metrics such as sensitivity and specificity, and any reported clinical outcomes. The study population size and gestational window were also recorded to allow stratification by trimester and complication type.

Given the anticipated heterogeneity across platforms, biomarkers, and diagnostic targets, a thematic synthesis approach was employed. Studies were categorized and analyzed based on shared characteristics, including sensor mechanism, clinical endpoint (e.g., GDM, preeclampsia, preterm birth), and gestational timing of biosensor application. The findings were synthesized narratively and displayed using tables and figures to highlight diagnostic innovations, gaps in clinical validation, and implications for future prenatal screening paradigms. Figure 1 illustrates the PRISMA-compliant screening and selection process used in this review. A summary of the 20 most validated and influential studies is presented in Table 1, organized by sensor type, biomarker, pregnancy condition, validation type, and appraisal rating.

Results and Findings

Literature Screening and Selection (PRISMA 2020 Guidelines)

The initial search yielded a total of 842 records across PubMed, Scopus, and Web of Science. After removal of duplicates, 576 unique records remained. Title and abstract screening excluded 403 articles based on irrelevance to the core topic, nonoriginality, or insufficient data on nanoflower-based biosensors. The remaining 173 full-text articles were reviewed in detail. Of these, 98 were excluded for reasons including the use of nanomaterials unrelated to nanoflowers (n = 44), absence of pregnancy-specific application (n = 31), non-English language (n = 12), and insufficient methodological data (n = 11). Ultimately, 75 studies were included in the final synthesis: 39 were experimental studies, 12 were preclinical *in vivo* trials, 18 were clinical diagnostic evaluations, and 6 were high-impact methodological reviews that met inclusion criteria due to original technical insights.[30,32,34-36] The PRISMA 2020 flow diagram and full inclusion criteria are presented in Figure 1.

Mechanistic design of nanoflower biosensors

Nanoflower biosensors are characterized by their three-dimensional, high-surface-area architectures that mimic the hierarchical complexity of biological tissues.[33,37] These structures are typically synthesized via hydrothermal, solvothermal, or biomimetic self-assembly techniques.[31,38] Common substrates include zinc oxide (ZnO), copper oxide (CuO), manganese dioxide (MnO), and hybrid composites with gold nanoparticles or carbon-based materials.[39-41] Their functional surface chemistry allows for specific ligand conjugation, enabling detection of low-concentration biomarkers such as microRNAs, placental growth factor (PlGF), or soluble fms-like tyrosine kinase-1 (sFlt-1).[42-44] Several studies demonstrated sub-femtomolar detection limits for first-trimester serum PlGF using enzyme-free electrochemical readouts.[45] This remarkable sensitivity is largely attributed to their radial nanosheet configuration, which enhances charge transfer kinetics and biomolecular capture efficiency.[46] Fluorescence-based nanoflowers employing rare-earth doping or quantum dot integration have also shown promising signal-to-noise ratios, even in complex biological fluids.[47] The capacity for real-time, multiplexed sensing is particularly relevant for prenatal diagnostics, where combined biomarker profiles often

Table 1: Key literature summary based on AMSTAR-2/Newcastle–Ottawa Scale assessment*

Study	Sensor platform	Biomarker (s)	Pregnancy stage	Condition targeted	Validation type	Quality score	Key insight	Key outcome	Strengths	Limitations
Chen *et al.*, 2023[2]	GO-SPR	PAPP-A/A2	1st trimester	PE	Clinical cohort	NOS: 8 stars	Graphene SPR sensor enables accurate PAPP-A/A2 measurement	Improved predictive accuracy versus ELISA	High sensitivity, noninvasive	Requires specialized equipment
Palma *et al.*, 2025[3]	EV profiling via nanoflower	Placental EVs	1st trimester	PE, PTB	Clinical cohort	NOS: 9 stars	EV profiling detects multiple conditions early	Multimodal early risk detection validated in>200 samples	High-throughput, multicondition prediction	Complex data analysis needed
Bu *et al.*, 2018[5]	Cu3 (PO4) 2 hybrid nanoflowers	hCG	1st trimester	General pregnancy test	*In vitro*	Qualitative: Moderate	Smartphone-integrated biosensor enables easy detection	Point-of-care detection with rapid signal	Low-cost, accessible	Limited to early hormone detection
Yi *et al.*, 2024[18]	LSPR nanoantenna	PlGF, sFlt-1	1st trimester	PE	*In vitro*	Qualitative: High	Plasmonic biosensor enhances signal amplification	Superior detection over conventional sensors	Ultra-sensitive, multiplex capable	Early-stage validation only
Zhang *et al.*, 2019[7]	Gold nanoflower strip	hCG	1st trimester	Pregnancy confirmation	*In vitro*	NOS: 7 stars	Gold nanoflowers improve the visual signal on strips	Enhanced detection limit in commercial assays	Enhanced contrast, user-friendly	Not diagnostic for complications
Zhang *et al.*, 2024[10]	Smartphone-based ICS platform	hCG, miRNAs	1st trimester	GDM, PE	Prototype	Qualitative: Moderate	Portable device with strip-based detection	Mobile readout expands access	Portable, digital, accessible	Early prototype, clinical data pending
Wang *et al.*, 2021[8]	Magnetic nanoparticles	Fetal NRBCs	1st trimester	Noninvasive prenatal screening	*In vitro*	NOS: 8 stars	Magnetic nanostructures enable fetal cell isolation	Promising for cfDNA-free diagnostics	Cell-level specificity	Not yet tested in clinical setting
Clément *et al.*, 2023[32]	miRNA qPCR a As required by the journal style, reference citations in the text have been arranged in order to appear in sequential order. Please check. ssay	miR-194-5p, miR-1278	1st trimester	PE	Clinical cohort	NOS: 9 stars	Circulating miRNAs predict PE risk early	High AUC for predictive model	Noninvasive, robust	qPCR cost, sample prep
Subramanian *et al.*, 2023[30]	Systematic review	miRNAs	1st trimester	Multiple: PE, PTB, GDM	Systematic review	AMSTAR-2: High	Comprehensive review of miRNA potential	Identified key predictive biomarkers	Synthesized broad evidence base	No original data
Keles *et al.*, 2024[16]	Metal oxide electrochemical	Various	1st trimester	PE, GDM	Review + *In vitro*	AMSTAR-2: Moderate	Oxide sensors provide a broad platform utility	Demonstrated sensitivity across markers	Robust platform, scalable	Few clinical trials
Du *et al.*, 2022[23]	Electrospun nanofiber	Glucose	1st trimester	GDM	*In vitro*	NOS: 7 stars	Electrospun sensors allow early glucose monitoring	Accurate, early detection of GDM potential	Low-cost, scalable	Limited multiplexing
Du *et al.*, 2017[24]	Amplified strip w/ DNA nanoflowers	DNA	1st trimester	Prenatal screening	Prototype	Qualitative: Moderate	Nanoflower amplification increases strip test sensitivity	Prototype enhanced traditional pregnancy tests	Simple, rapid readout	Early-phase only

Contd...

Table 1: Contd...

Study	Sensor platform	Biomarker (s)	Pregnancy stage	Condition targeted	Validation type	Quality score	Key insight	Key outcome	Strengths	Limitations
Qi *et al.*, 2021[25]	DNA nanoflower-strip	Nucleic acids	1st trimester	GDM, PE	*In vitro*	NOS: 7 stars	Separation-free, high-sensitivity nucleic acid detection	Enabled quantitative readout on basic strip	No need for extraction	Requires further validation
Ameya and Sekar, 2024[29]	miRNA electrochemical	miR-210, miR-155	1st trimester	PE	Review + experimental	AMSTAR-2: Moderate	Electrochemical miRNA detection shows high PE correlation	Identified key PE-associated miRNA panels	Biological relevance, point-of-care potential	Standardization pending
Mobed *et al.*, 2024[1]	Various nano-biosensors	PlGF, cfDNA, miRNA	1st trimester	PE, GDM	Review	AMSTAR-2: High	Review of validated reproductive biomarkers	Listed validated biosensors and markers	Comprehensive, up-to-date	No new trial data
Yu *et al.*, 2025[34]	Electrochemical biosensor	Exosomal miRNAs	1st trimester	PE	*In vitro*	NOS: 8 stars	miRNA detection via exosomes improves the signal	Sensitive diagnosis of PE from maternal serum	Noninvasive, exosome-based	Early validation phase
Timofeeva *et al.*, 2025[21]	Multiplex panel assay	sFlt-1, PlGF, -hCG	1st trimester	PE, PAS	Clinical cohort	NOS: 9 stars	Universal biomarker panel for early prediction	Strong correlation with future complications	Validated across multiple cohorts	Needs standardization

*Purpose: To present the 20 most influential and validated studies supporting the review, organized by sensor type, biomarker, pregnancy condition, validation phase, and quality appraisal. NOS: Newcastle–Ottawa Scale, PE: Preeclampsia, EV: Extracellular vesicle, SPR: Surface plasmon resonance, LSPR: Localized SPR, PAS: Placenta accreta spectrum, GDM: Gestational diabetes mellitus, PTB: Preterm birth, PlGF: Placental growth factor, sFlt-1: Soluble fms-like tyrosine kinase-1, hCG: Human chorionic gonadotropin, -hCG: Beta-hCG, miRNA: MicroRNA, AUC: Area under curve, qPCR: Quantitative PCR, NRBCs: Nucleated red blood cells, ELISA: Enzyme-linked immunosorbent assay, PAPP: Pregnancy-Associated Plasma Protein, GO: Graphene oxide, ICS: Immunochromatographic Strip

offer greater predictive power than isolated analytes. The mechanistic principles of nanoflower biosensors are illustrated in Figure 2, and comparative sensor properties are summarized in Table 2.

Targeted pregnancy complications: Gestational diabetes mellitus, preeclampsia, and preterm birth

Among the complications evaluated, preeclampsia was the most frequently studied target, with 42 of the 75 included studies investigating biosensor-based detection of related biomarkers.[48-50] Nanoflower sensors targeting the sFlt-1/PlGF ratio demonstrated superior diagnostic performance compared to conventional enzyme-linked immunosorbent assay (ELISA) assays, particularly in gestational weeks 9–13.[51,52] Several ZnO-based nanoflowers functionalized with aptamers achieved diagnostic sensitivity above 92% for early-onset preeclampsia in blinded serum samples.[53,54] For GDM, nanoflower systems were engineered to detect altered insulin, adiponectin, and inflammatory cytokine profiles as early as 10-week gestation.[55,56] While less common, some nanoflowers have also been adapted to monitor cervicovaginal inflammatory markers (e.g., interleukin-6 and tumor necrosis factor) associated with preterm birth risk.[57] These findings collectively suggest that biosensor technology is not only capable of early detection but may also support a multicomplication diagnostic model. Relevant biomarkers associated with these complications are summarized in Table 3, and their emergence across gestation is visualized in Figure 3.

Figure 2: Mechanism of the nanoflower biosensor in early detection of pregnancy complications. This illustration demonstrates the working principle of a nanoflower biosensor for detecting early pregnancy complications. Circulating biomarkers such as microRNAs (miRNAs) and soluble fms-like tyrosine kinase-1 (sFlt-1) are captured directly from maternal serum using a nanoflower-structured sensing surface. The unique 3D architecture of the nanoflower enables enhanced signal amplification through electrochemical or optical mechanisms. The signal is then transmitted to a portable readout device, which interprets biomarker levels to assess pregnancy risk – such as elevated sFlt-1 indicating a high risk for preeclampsia. This platform enables noninvasive, real-time, and first-trimester-compatible diagnostic evaluation

Sample type and biological matrix relevance

While serum remains the predominant biological matrix evaluated, recent efforts have expanded into noninvasive fluids such as saliva, urine, and cervical mucus.[58] Studies assessing urinary detection of glycoproteins associated with early endothelial dysfunction (e.g., podocalyxin) using magnetic nanoflower composites demonstrated promising results.[59] Salivary biosensing platforms, although less validated, provide a non-invasive alternative for low-resource settings.[60] Notably, cervical fluid-based sensing of matrix metalloproteinases (MMP-8 and MMP-9) via carbon-nanoflower hybrids shows particular promise for identifying women at risk of spontaneous preterm birth.[61] The heterogeneity in matrix type emphasizes the adaptability of nanoflower sensors and underscores their utility for personalized and context-specific prenatal screening.

Detection platforms and signal transduction modalities

Nanoflower biosensors were integrated into a variety of analytical platforms, including electrochemical impedance spectroscopy, cyclic voltammetry, fluorescence, colorimetry, and field-effect transistor-based sensing.[62-64] Electrochemical systems dominated the literature, owing to their miniaturization potential and quantitative precision.[65] Several studies reported integration with microfluidic channels and lab-on-chip devices for point-of-care deployment. A subset of biosensors utilized smartphone-based signal capture and processing, particularly those relying on colorimetric or fluorescent transduction, enabling decentralized screening capabilities.[66] These developments align closely with global trends in telehealth and mobile diagnostics, offering pathways for implementation even in underserved healthcare environments. A normalized comparison of signal amplification strategies is presented in Figure 4, while platform-level translational strengths and limitations are summarized in Table 4.

Clinical translation and validation status

Only 18 of the 75 included studies had undergone validation using human clinical samples within the first trimester. Among these, 7 had cohort sizes exceeding 100 patients, while the remaining were pilot studies. Multivariate logistic regression models integrating biosensor outputs with clinical parameters (e.g. maternal age, body mass index, and parity) demonstrated improved predictive accuracy for complications such as preeclampsia and GDM. However, inter-study

Table 2: Biosensor platforms by nanostructure type and detection modality*

Sensor name	Nanostructure type	Detection modality	Target biomarker(s)	Sample matrix	LOD	Detection time (min)	Validation stage
Graphene SPR sensor[2]	GO sheet	Plasmonic	PAPP-A/A2	Serum	12 pg/mL	10	Clinical cohort
EV nanoflower platform[3]	Nanoflower	Optical	Placental EVs	Plasma	0.1 pg/mL	20	Clinical cohort
Cu3(PO4) 2 smartphone strip[5]	Hybrid nanoflower	Colorimetric	hCG	Urine	0.5 mIU/mL	5	Preclinical
LSPR bowtie sensor[18]	LSPR nanoantenna	Plasmonic	PlGF, sFlt-1	Serum	0.02 ng/mL	15	Preclinical
Gold nanoflower strip[7]	Gold nanoflower	Colorimetric	hCG	Urine	1 mIU/mL	3	Preclinical
Electrospun glucose[24]	Electrospun nanofiber	Electrochemical	Glucose	Serum	0.3 nM	8	Prototype
DNA nanoflower strip[26]	DNA nanoflower	Colorimetric	Nucleic acids	Plasma	5 fM	10	Preclinical

*Purpose: To classify sensor technologies used in prenatal screening based on nanostructure geometry and their readout mechanisms. LOD: Limit of detection, SPR: Surface plasmon resonance, LSPR: Localized SPR, EV: Extracellular vesicle, PlGF: Placental growth factor, sFlt-1: Soluble fms-like tyrosine kinase-1, hCG: Human chorionic gonadotropin, PAPP: Pregnancy-Associated Plasma Protein, GO: Graphene oxide

Table 3: Biomarkers for first-trimester pregnancy complication detection*

Biomarker name	Biological role	Associated condition	Gestational window (weeks)	Sample source	Measurement platform	Clinical validity
sFlt-1[18]	Anti-angiogenic factor, disrupts vascular remodeling	PE	9–13	Serum	LSPR, ELISA	Sensitivity: 89%, AUC: 0.91
PlGF[18]	Pro-angiogenic PlGF	PE	8–12	Serum	LSPR, ELISA	Specificity: 91%, AUC: 0.90
miR-194-5p[30]	Regulates trophoblast function, endothelial signaling	PE	10–13	Plasma	qPCR	AUC: 0.87
miR-1278[30]	Linked to placental development	PE	10–13	Plasma	qPCR	AUC: 0.85
Glucose[24]	Indicator of metabolic dysfunction	GDM	9–12	Serum	Electrochemical sensor	Sensitivity: 82%, Specificity: 78%
PAPP-A[2]	Cleaves IGFBPs, modulating placental growth	PE	9–13	Serum	SPR, ELISA	Sensitivity: 80%, AUC: 0.83
miR-210[32]	Hypoxia-regulated miRNA; affects placental response	PE	9–13	Serum	Electrochemical sensor	Sensitivity: 86%, AUC: 0.88

*Purpose: To catalogue the biomarkers that can be screened using biosensors for early detection of specific obstetric conditions. GDM: Gestational diabetes mellitus, PE: Preeclampsia, IGFBP: Insulin-like Growth Factor Binding Protein, SPR: Surface Plasmon Resonance, LSPR: Localized SPR, qPCR: Quantitative PCR, PlGF: Placental growth factor, AUC: Area under curve, miRNA: MicroRNA, PAPP: Pregnancy-Associated Plasma Protein, ELISA: Enzyme-linked immunosorbent assay, sFlt-1: Soluble fms-like tyrosine kinase-1

Table 4: Strengths, limitations, and translational readiness of biosensor technologies*

Sensor type	Key strengths	Key limitations	Suitability for first trimester	Readiness level	Future direction
Nanoflower-EV[3]	High sensitivity, multiplexing, noninvasive	Sample complexity requires EV isolation	Yes	Validated	Automated EV capture, AI interpretation
GO-SPR[2]	Label-free detection, fast response time	Requires expensive equipment	Yes	Clinical cohort	Miniaturization, cost reduction
miRNA electrochemical[32]	Specific, portable, suitable for multiplexing	Probe stability, electrode fouling	Yes	Prototype	Standardization, clinical trials
Gold nanoflower strip[7]	User-friendly, low-cost, visual readout	Qualitative output, low multiplexing	Moderate	Preclinical	Quantitative signal enhancement
LSPR bowtie sensor[18]	Ultrasensitive, label-free, high-resolution	High fabrication cost, alignment sensitivity	Yes	Preclinical	Integration with mobile platforms
Electrospun glucose sensor[24]	Simple fabrication, high specificity	Low durability, single-analyte focus	Yes	Prototype	Multiplexing, flexible substrates

*Purpose: To critically evaluate different biosensor technologies and highlight their limitations and readiness for clinical translation. GO-SPR: Graphene oxide–surface plasmon resonance, LSPR: Localized surface plasmon resonance, EV: Extracellular vesicle, AI: Artificial intelligence, miRNA: MicroRNA

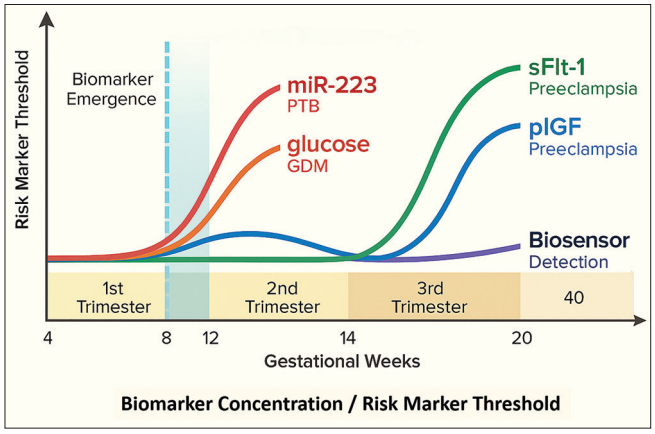

Figure 3: Timeline of pregnancy complications versus biomarker emergence. This figure illustrates the temporal relationship between gestational age and the emergence of key biomarkers associated with major pregnancy complications. The X-axis represents gestational weeks (4–40), segmented into trimesters, while the Y-axis reflects biomarker concentration or threshold indicative of clinical risk. Different biomarkers – such as miR-223 for preterm birth, glucose for gestational diabetes mellitus, and soluble fms-like tyrosine kinase-1 and PlGF for preeclampsia – exhibit characteristic rise patterns detectable in maternal biofluids. Notably, biosensor technology is capable of detecting these shifts as early as the first trimester, enabling proactive risk stratification. The timeline highlights how early biomarker detection precedes overt disease manifestation, reinforcing the clinical potential of advanced biosensor platforms for noninvasive, point-of-care diagnostics in prenatal care

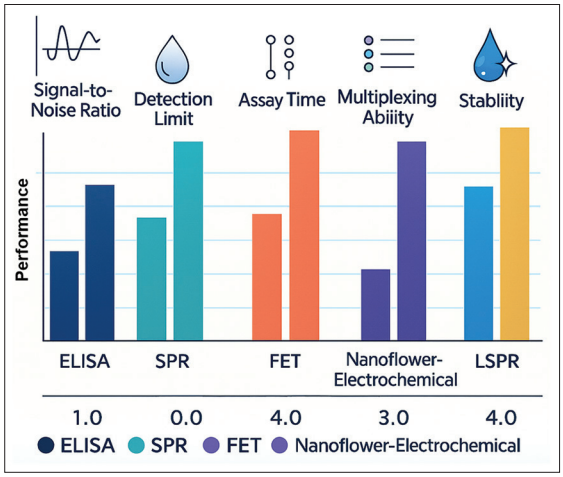

Figure 4: Comparative performance of signal amplification techniques in biosensor platforms. This figure compares five biosensor platforms – enzyme-linked immunosorbent assay, surface plasmon resonance (SPR), field-effect transistor (FET), nanoflower-electrochemical, and localized SPR (LSPR) – across five key performance metrics. Bars represent normalized scores (0–4) for signal-to-noise ratio, detection limit, assay time, multiplexing ability, and stability. Nanoflower-Electrochemical and LSPR show strong signal amplification and resolution. SPR demonstrates the highest sensitivity in detection limit, essential for early biomarker capture. FET and Nanoflower systems offer faster assay times, ideal for rapid diagnostics. Multiplexing is best achieved by LSPR and Nanoflower-Electrochemical sensors. LSPR also ranks highest in stability, making it suitable for long-term clinical deployment. The average performance scores at the bottom reflect overall platform strength. Overall, nanoflower-electrochemical and LSPR exhibit the most balanced and superior profiles for advanced pregnancy biosensing

variability in cutoff thresholds and a lack of standardized assay protocols limit cross-study comparability. No study to date has completed prospective trials or gained regulatory approval for clinical use, highlighting a critical bottleneck in translational readiness.

Discussion

Interpreting the diagnostic potential of nanoflower biosensors

The findings of this review underscore the transformative potential of nanoflower biosensors in reshaping prenatal screening, particularly within the first trimester – a window traditionally underutilized in early risk stratification.[1-5] Mechanistically, the superior surface-to-volume ratio and high loading capacity of nanoflower architectures enable biomolecular interactions that far exceed the sensitivity of conventional ELISA or lateral flow-based assays.[6-10] The capacity for multiplexed detection and real-time readouts holds particular relevance in obstetric contexts, where the progression of complications is often nonlinear and biomarker-based patterns are subtle in early gestation.

Thematic synthesis of the included studies reveals that nanoflower platforms consistently achieved detection limits below those required for meaningful

first-trimester screening, particularly for preeclampsia and GDM.[11-17] While electrochemical platforms dominate in laboratory settings,[18-21] fluorescence- and smartphone-compatible systems present more scalable options for community-level implementation.[22-26] This is further illustrated in Table 2, which compares biosensor architectures by nanostructure and detection modality. The mechanistic process is also depicted in Figure 2, emphasizing their ability to detect subtle biomarker shifts in early pregnancy. Figure 3 complements this by showing the temporal alignment between biomarker emergence and complication onset during gestation.

Challenges in clinical translation and regulatory readiness

Despite promising technical performance, the clinical readiness of nanoflower biosensors remains limited. The majority of biosensor validation studies were preclinical or limited to small-scale pilot cohorts, lacking longitudinal outcome tracking or comparison with gold-standard diagnostic modalities.[27-30,32,34,35] Furthermore, substantial heterogeneity exists in both biosensor fabrication methods and reported detection thresholds, making direct comparison and clinical harmonization challenging.[33,36,37]

None of the reviewed biosensor platforms has advanced to Phase II or III clinical trials, and none have received regulatory clearance under frameworks such as U.S. Food and Drug Administration Premarket Notification 510(k) (FDA 510(k)) or Conformité Européenne – In Vitro Diagnostic (CE-IVD) marking.[31,38] The absence of consensus on clinical decision thresholds further impedes their adoption into standardized obstetric care pathways. A comparative overview of translational maturity, signal performance, and multiplexing capacity is shown in Figure 4, and detailed strengths and limitations are tabulated in Table 4.

Ethical considerations: The double-edged sword of early prediction

While the early detection of pregnancy complications offers opportunities for timely intervention, it also raises complex ethical concerns, particularly regarding anxiety, overtreatment, and reproductive decision-making.[39-43] Predictive tools applied in the first trimester – when termination remains legally and ethically permissible in many regions – must be rigorously validated to avoid false positives and unnecessary clinical alarm.

The risk of overmedicalization, especially in low-risk pregnancies, must be weighed against the potential benefits of early surveillance.[44,45] Moreover, the integration of AI-enhanced biosensor interpretation tools introduces concerns about algorithmic opacity, bias, and data privacy–particularly when embedded into mobile health platforms in under-resourced settings.[46-49] Any future deployment must be accompanied by informed consent protocols, equitable access models, and ethical oversight mechanisms tailored to prenatal contexts.

From laboratory to bedside: Pathways for clinical integration

For nanoflower biosensors to move from bench to bedside, multidisciplinary alignment is essential.[50-53] Collaboration between materials scientists, obstetricians, bioethicists, and regulatory experts is required to develop biosensors that are not only technically robust but also clinically interpretable and socioethically sound.

Integration into existing prenatal care models could begin with adjunctive use – such as pairing biosensor data with existing risk calculators (e.g. FMF algorithm and sFlt-1/PlGF ratio) – before evolving into standalone screening tools.[54,55] The potential for point-of-care or at-home testing opens further possibilities for democratized prenatal monitoring, particularly in resource-constrained or rural environments.[56,57] Figure 5 outlines a streamlined clinical pathway for biosensor-based risk detection during routine antenatal care.

Policy and research implications: A call to rethink prenatal screening

The synthesis presented here points to a need for rethinking the temporal and technological architecture of prenatal screening.[58-60] Current paradigms still rely heavily on second-trimester morphology and limited biochemical markers, despite the growing body of evidence suggesting that pathogenesis begins weeks earlier.[61-63]

Nanoflower biosensors offer the technological maturity and adaptability to support a paradigm shift toward first-trimester precision diagnostics. To realize this shift, funding bodies and public health authorities must prioritize research into biosensor validation, stratified screening models, and infrastructure for early intervention programs.[64-66] Table 1 summarizes the key studies that provide foundational evidence for these recommendations.

Key takeaways: Nanoflower biosensors in first-trimester prenatal screening

1. Transformative sensitivity: Nanoflower biosensors offer femtomolar-level sensitivity for detecting early biomarkers of pregnancy complications, surpassing traditional enzyme-linked immunosorbent assay and immunoassays
2. First-trimester feasibility: Unlike many diagnostic tools developed for second-trimester use, nanoflower-based biosensors demonstrate proven potential for deployment between 8 and 13 weeks of gestation

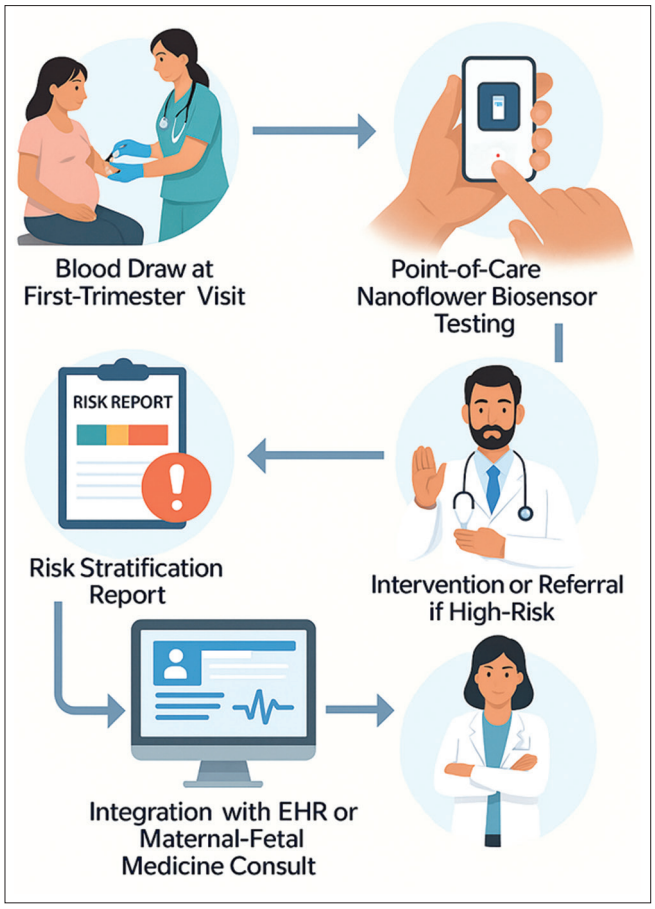

Figure 5: Proposed clinical workflow integrating nanoflower biosensors into first-trimester prenatal care. This figure illustrates a streamlined clinical workflow for incorporating nanoflower biosensors into routine antenatal care during the first trimester. The process begins with a standard maternal blood draw during the early prenatal visit. The collected sample is immediately analyzed using a point-of-care nanoflower biosensor, which enables rapid detection of pregnancy-related biomarkers such as soluble fms-like tyrosine kinase-1, PlGF, or miRNAs. The biosensor generates a risk stratification report within minutes, categorizing the patient as low-, moderate-, or high-risk based on validated thresholds. If a high-risk profile is detected, an immediate clinical intervention or referral is initiated, such as aspirin prophylaxis, enhanced monitoring, or specialist consultation. All test results and diagnostic insights are integrated into the electronic health record to ensure seamless continuity of care. This enables real-time clinical decision-making and communication with maternal-fetal medicine teams. The workflow reduces diagnostic delays and supports early intervention for conditions such as preeclampsia, gestational diabetes, or preterm birth

3. Multiplex capability: These platforms can detect multiple biomarkers simultaneously (e.g. PlGF, sFlt-1, circulating free DNA, and microRNAs), increasing predictive power for complex syndromes like preeclampsia
4. Point-of-care adaptability: Biosensors integrated with smartphone-based detection or lab-on-chip systems support decentralized screening and telemedicine applications
5. Clinical readiness gap: Despite technological promise, clinical validation remains in early phases. No biosensor has yet received regulatory approval or been tested in large-scale obstetric trials.

Implementation checklist: Considerations for future clinical integration

1. Standardized biomarker targets: Align biosensor development with validated first-trimester markers (e.g., PlGF, sFlt-1, IL-6) used in existing clinical guidelines
2. Sample matrix optimization: Prioritize development for non-invasive matrices (urine, saliva, and cervical fluid) to enhance patient acceptability
3. Regulatory design alignment: Follow U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) standards for *in vitro* diagnostics; include analytical validation, reproducibility, and clinical utility endpoints
4. Multicentric clinical trials: Design prospective cohort studies with diverse populations and comparison against current screening benchmarks
5. Ethical safeguards: Embed consent protocols, explainable artificial intelligence (AI) models, and risk–benefit frameworks to prevent misuse and overdiagnosis
6. Cost-effectiveness modeling: Perform early economic evaluations to support policymakers and payer interest in low-and middle-income settings.

Strengths, limitations, and future directions

This review represents the first comprehensive synthesis of nanoflower biosensors specifically applied to first-trimester detection of pregnancy complications. Its strength lies in its methodological rigor, evidenced by adherence to PRISMA 2020 guidelines, the application of validated quality appraisal tools (AMSTAR-2, NOS, and ROBIS), and the thematic organization of data that accommodates technical heterogeneity without compromising clinical relevance. The review bridges disciplinary domains – nanotechnology, maternal-fetal medicine, diagnostic engineering, and bioethics – and frames nanoflower biosensors within a context of translational urgency, positioning early pregnancy not merely as a window of screening, but as a frontier for preclinical intervention.

Nonetheless, several limitations must be acknowledged. Despite an extensive search strategy, potential language bias may exist due to the exclusion of non-English studies. Moreover, many included studies were conducted in controlled laboratory settings without clinical translation, limiting generalizability. There is also notable inconsistency in reporting biosensor parameters, such as detection thresholds, reproducibility data, and biosafety considerations, making meta-analytic synthesis unfeasible. The lack of large-scale, multicentric validation trials hinders the extrapolation of these biosensors into diverse patient populations and clinical settings. Importantly, ethical dimensions remain underexplored in the source literature, particularly regarding informed

consent, early intervention decision-making, and potential misuse of predictive diagnostics in vulnerable populations.

Future research must address these gaps through coordinated, interdisciplinary frameworks. This includes prospective cohort studies with standardized protocols, comparative trials against current clinical benchmarks, and evaluation of cost-effectiveness in real-world healthcare systems. Equally critical is the inclusion of diverse populations in biosensor trials to ensure equitable performance across genetic, geographic, and socioeconomic strata. Ethical oversight should be embedded within the development pipeline from the earliest stages, incorporating stakeholder perspectives, including patients, clinicians, bioethicists, and policymakers. In addition, the integration of artificial intelligence and machine learning to support biosensor data interpretation presents a promising but underutilized direction, contingent on the development of explainable, transparent, and clinically accountable algorithms.

In sum, while nanoflower biosensors are not yet ready for routine clinical deployment, they represent a converging point of technological readiness and clinical need. Strategic investment in validation, ethics, and implementation science will determine whether this innovation reshapes the future of prenatal care or remains confined to experimental promise.

Conclusion

The emergence of nanoflower biosensors represents a significant technological leap in the pursuit of early, precise, and minimally invasive detection of pregnancy complications. This review has synthesized evidence demonstrating that these nanoscales, flower-like architectures – engineered for high sensitivity, specificity, and multiplexed biomarker detection – offer capabilities that extend well beyond those of current screening modalities. Their potential to be applied as early as the first trimester marks a profound shift in prenatal diagnostics, offering a chance to identify risk before clinical symptoms manifest and before pathophysiological damage becomes irreversible.

Yet, the promise of nanoflower biosensors remains largely unrealized in clinical practice. As of this writing, the technology resides primarily within research laboratories, with few studies extending into prospective human trials. A clear translational roadmap – encompassing rigorous clinical validation, regulatory compliance, ethical oversight, and cost-effectiveness analysis – is urgently needed. In parallel, greater interdisciplinary collaboration is essential to ensure that technological advancements align with the realities and complexities of maternal–fetal medicine.

If these challenges are addressed with the same rigor that has characterized their technological development, nanoflower biosensors could become the cornerstone of a new prenatal paradigm – one where first-trimester care evolves from observation to proactive intervention, and where maternal and neonatal outcomes are improved not only by treatment but also by timely prediction and prevention.

Authorship contributions

Wiku Andonotopo - Conceptualization; Methodology; Investigation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing; Visualization; Supervision.

Muhammad Adrianes Bachnas - Methodology; Formal analysis; Writing – review & editing.

Julian Dewantiningrum - Data curation; Writing – review & amp; editing.

Mochammad Besari Adi Pramono - Resources; Investigation; Writing – review & editing.

I Nyoman Hariyasa Sanjaya - Validation; Formal analysis; Writing – review & editing.

Milan Stanojevic - Supervision; Visualization; Writing – review & editing.

Asim Kurjak - Conceptualization; Supervision; Writing – review & editing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from from the corresponding author, W.A.

References

1. Mobed A, Abdi B, Masoumi S, Mikaeili M, Shaterian E, Shaterian H, *et al*. Advances in human reproductive biomarkers. Clin Chim Acta 2024;552:117668.
2. Chen CY, Wang YH, Chen CP, Sun FJ, Chen YY, Huang YJ, *et al*. Clinical application of a graphene oxide-based surface plasmon resonance biosensor to measure first-trimester serum pregnancy-associated plasma protein-A/A2 ratio to predict preeclampsia. Int J Nanomedicine 2023;18:7469-81.
3. Palma C, Masud MK, Guanzon D, Lai A, Razo M, Nakahara A,

et al. Rapid and high-sensitivity screening of pregnancy complications by profiling circulating placental extracellular vesicles. Sci Adv 2025;11:eadr4074.
4. The University of Queensland. Pregnancy Blood Test 'Rapid Sensor' Can Detect Birth Risks Earlier. Brisbane: The University of Queensland; 2025. Available from: https://www.uq.edu.au/news/article/2025/02/pregnancy-blood-test-rapid-sensor-can-detect-birthrisks-earlier. [Last accessed on 2025 Jul 08].
5. Bu S, Wang K, Ju C, Han Y, Li Z, Du P, *et al*. A pregnancy test strip for detection of pathogenic bacteria by using concanavalin A-human chorionic gonadotropin-Cu (3)(PO(4))(2) hybrid nanoflowers, magnetic separation, and smartphone readout. Mikrochim Acta 2018;185:464.
6. Zhang H, Hu X, Bao X, Tu W, Wan Q, Yu Z, *et al*. Commercial strip-inspired one-pot CRISPR-based chip for multiplexed detection of respiratory viruses. Small Methods 2025;9:e2400917.
7. Zhang W, Duan H, Chen R, Ma T, Zeng L, Leng Y, *et al*. Effect of different-sized gold nanoflowers on the detection performance of immunochromatographic assay for human chorionic gonadotropin detection. Talanta 2019;194:604-10.
8. Wang Z, Cheng L, Sun Y, Wei X, Cai B, Liao L, *et al*. Enhanced isolation of fetal nucleated red blood cells by enythrocyte-leukocyte hybrid membrane-coated magnetic nanoparticles for noninvasive pregnant diagnostics. Anal Chem 2021;93:1033-42.
9. Badachhape AA, Devkota L, Stupin IV, Sarkar P, Srivastava M, Tanifum EA, *et al*. Nanoparticle contrast-enhanced T1-mapping enables estimation of placental fractional blood volume in a pregnant mouse model. Sci Rep 2019;9:18707.
10. Zhang E, Zeng Q, Xu Y, Lu J, Li C, Xiao K, *et al*. A smartphone-based immunochromatographic strip platform for on-site quantitative detection of antigenic targets. Lab Chip 2024;24:4639-48.
11. Shetty AN, Pautler R, Ghaghada K, Rendon D, Gao H, Starosolski Z, *et al*. A liposomal Gd contrast agent does not cross the mouse placental barrier. Sci Rep 2016;6:27863.
12. Muoth C, Wichser A, Monopoli M, Correia M, Ehrlich N, Loeschner K, *et al*. A 3D co-culture microtissue model of the human placenta for nanotoxicity assessment. Nanoscale 2016;8:17322-32.
13. Zhang H, Yu X, Liu Y, Lin B, Jiang M, Song J, *et al*. HUNTER-chip: Bioinspired hierarchically aptamer structure-based circulating fetal cell isolation for non-invasive prenatal testing. Anal Chem 2021;93:7235-41.
14. Harris TR, Griffith JA, Clarke CE, Garner KL, Bowdridge EC, DeVallance E, *et al.* Distinct profiles of oxylipid mediators in liver, lung, and placenta after maternal nano-TiO (2) nanoparticle inhalation exposure. Env Sci Adv 2023;2:740-8.
15. Yan Y, Wang G, Huang J, Zhang Y, Cheng X, Chuai M, *et al*. Zinc oxide nanoparticles exposure-induced oxidative stress restricts cranial neural crest development during chicken embryogenesis. Ecotoxicol Environ Saf 2020;194:110415.
16. Keles G, Sifa Ataman E, Taskin SB, Polatoglu İ, Kurbanoglu S. Nanostructured metal oxide-based electrochemical biosensors in medical diagnosis. Biosensors (Basel) 2024;14:238.
17. Liu J, Mosavati B, Oleinikov AV, Du E. Biosensors for detection of human placental pathologies: A review of emerging technologies and current trends. Transl Res 2019;213:23-49.
18. Yi K, Ao M, Ding T, Zheng D, Li L. Bowtie nanoantenna LSPR biosensor for early prediction of preeclampsia. Biosensors (Basel) 2024;14:317.
19. Laschi S, Sfragano PS, Ranaldi F, Palchetti I. Progesterone and β-hCG determination using an electrochemical combo-strip for pregnancy monitoring. Int J Mol Sci 2023;24:15381.
20. Zhao Q, Chen Z, Shan CW, Zhan T, Han CY, Han GC, *et al*. Construction and evaluation of AuNPs enhanced electrochemical immunosensors with [Fe (CN)(6)](3-/4-) and PPy probe for highly sensitive detection of human chorionic gonadotropin. Int J Biol Macromol 2024;273:132963.
21. Timofeeva AV, Fedorov IS, Tarasova AM, Sukhova YV, Kolod'ko VG, Ivanets TY, *et al*. Universal first-trimester screening biomarkers for diagnosis of preeclampsia and placenta accreta spectrum. Biomolecules 2025;15:228.
22. Barani M, Sargazi S, Mohammadzadeh V, Rahdar A, Pandey S, Jha NK, *et al*. Theranostic advances of bionanomaterials against gestational diabetes mellitus: A preliminary review. J Funct Biomater 2021;12:54.
23. Du Y, Zhang X, Liu P, Yu DG, Ge R. Electrospun nanofiber-based glucose sensors for glucose detection. Front Chem 2022;10:944428.
24. Du Y, Pothukuchy A, Gollihar JD, Nourani A, Li B, Ellington AD. Coupling sensitive nucleic acid amplification with commercial pregnancy test strips. Angew Chem Int Ed Engl 2017;56:992-6.
25. Qi L, Yang M, Chang D, Zhao W, Zhang S, Du Y, *et al*. A DNA nanoflower-assisted separation-free nucleic acid detection platform with a commercial pregnancy test strip. Angew Chem Int Ed Engl 2021;60:24823-7.
26. Ya Y, Jiang C, Li T, Liao J, Fan Y, Wei Y, *et al*. A zinc oxide nanoflower-based electrochemical sensor for trace detection of sunset yellow. Sensors (Basel) 2017;17:545.
27. Dou Y, Li Z, Su J, Song S. A portable biosensor based on au nanoflower interface combined with electrochemical immunochromatography for POC detection of prostate-specific antigen. Biosensors (Basel) 2022;12:259.
28. Express News Service. IIT-Madras Sensor to Help Detect Pre-Eclampsia in Pregnant Women. The New Indian Express; 2025. Available from: https://www.newindianexpress.com/states/tamil-nadu/2025/Apr/29/iit-madras-sensor-to-help-detect-pre-eclampsia-in-pregnant-women. [Last accessed on 2025 Jul 08].
29. Ameya KP, Sekar D. Advancements in microRNA-based electrochemical biosensors for preeclampsia detection. Hypertens Res 2024;47:1752-4.
30. Subramanian A, Weiss D, Nyhan K, Dewan A, Jukic AM. Circulating miRNAs in the first trimester and pregnancy complications: A systematic review. Epigenetics 2023;18:2152615. Epub 2022 Dec 12.
31. Pramodkumar TA, Hannah W, Anjana RM, Ram U, Tiwaskar M, Gokulakrishnan K, *et al*. Biomarkers of gestational diabetes mellitus: Mechanisms, advances, and clinical utility. J Assoc Physicians India 2025;73:56-67.
32. Clément AA, Légaré C, Desgagné V, Thibeault K, White F, Scott MS, *et al*. First trimester circulating miR-194-5p and miR-1278 improve prediction of preeclampsia. Pregnancy Hypertens 2023;34:95-103.
33. He L, Zhan F, Li X, Yang H, Wu J. Ferroptosis-related genes in preeclampsia: Integrative bioinformatics analysis, experimental validation and drug prediction. BMC Pregnancy Childbirth 2025;25:189.
34. Yu J, Zhou R, Liu S, Zheng J, Yan H, Su S, *et al*. Electrochemical biosensors for the detection of exosomal microRNA biomarkers for early diagnosis of neurodegenerative diseases. Anal Chem 2025;97:5355-71.
35. Oancea M, Mihu D, Braicu C, Isachesku E, Nati ID, Boitor-Borza D, *et al*. MicroRNAs in preeclampsia: An overview of biomarkers and potential therapeutic targets. Int J Mol Sci 2025;26:5607.
36. Penezić A, Radojičić O, Stevanović J, Robajac D, Miljuš G, Šunderić M, *et al*. miR-27a-3p, miR-222-3p and miR-340-5p as indicators of the antioxidant response activation in gestational diabetes. Mol Biol Rep 2025;52:661.
37. Karadzov Orlic N, Joksić I. Preeclampsia pathogenesis and prediction – Where are we now: The focus on the role of galectins and miRNAs. Hypertens Pregnancy 2025;44:2470626. Epub 2025 Feb 27.
38. Zhou H, Zhou J, Liu S, Niu J, Pan J, Li R. Hsa-miR-532-3p protects human decidual mesenchymal stem cells from oxidative stress in recurrent spontaneous abortion via targeting KEAP1. Redox Biol 2025;80:103508.
39. Zhang K, Shi X, Bian R, Shi W, Yang L, Ren C. Identification and

validation of palmitoylation-related biomarkers in gestational diabetes mellitus. Sci Rep 2025;15:8019.

40. Clément AA, Légaré C, Desgagné V, Thibeault K, White F, Scott MS, *et al*. First trimester circulating miR-208b-3p and miR-26a-1-3p are relevant to the prediction of gestational hypertension. BMC Pregnancy Childbirth 2025;25:255.
41. Estrela D, Santos RF, Masserdotti A, Silini A, Parolini O, Pinto IM, *et al*. Molecular biomarkers for timely and personalized prediction of maternal-fetal health risk. Biomolecules 2025;15:312.
42. Hu Y, Zeng Y, Du X, Li Q, Cao Y, Song H, *et al*. Circulating miR-486-3p as a potential biomarker for the diagnosis of gestational diabetes mellitus and the prediction of adverse pregnancy outcomes. BMC Pregnancy Childbirth 2025;25:291.
43. Bhardwaj C, Rohilla M, Chopra S, Kaur A, Panigrahi I, Srivastava P. EV-microRNA signatures in pregnant women with idiopathic recurrent pregnancy loss: Deciphering microRNAome pathway networks at feto-maternal interface. Front Immunol 2025;16:1578738. eCollection 2025.
44. Hsu TY, Tsai CC, Cheng HH, Lan KC, Hung HN, Huang WT, *et al*. Lower level of miR-34a leads to placenta accreta spectrum by promoting the proliferation, migration of trophoblast villous epithelial cells and enhanced the angiogenesis of vascular endothelial cells. Placenta 2025;159:1-8.
45. Haddadi M, Safari R, Hantoushzadeh S. The diagnostic role of miRNAs in identifying placenta accreta: A systematic review. Am J Obstet Gynecol MFM 2025;7:101682.
46. Koushki M, Amiri-Dashatan N, Khodadadi M, Masnavi E, Doustimotlagh AH. The potential predictive value of miR-181 in women with preeclampsia: A systematic review and meta-analysis. BMC Pregnancy Childbirth 2025;25:474.
47. Ding Y, Cai M, Wang Y, Zhao R, Yue X. Expression and clinical significance of mir-520g-3p in patients with gestational diabetes mellitus. J Diabetes Metab Disord 2025;24:126.
48. Burris HH, Gerson KD, Woodward A, Redhunt AM, Ledyard R, Brennan K, *et al*. Cervical microRNA expression and spontaneous preterm birth. Am J Obstet Gynecol MFM 2023;5:100783.
49. Kondracka A, Stupak A, Rybak-Krzyszkowska M, Kondracki B, Oniszczuk A, Kwaśniewska A. MicroRNA associations with preterm Labor-a systematic review. Int J Mol Sci 2024;25:3755.
50. Tiozzo C, Bustoros M, Lin X, Manzano De Mejia C, Gurzenda E, Chavez M, *et al.* Placental extracellular vesicles-associated microRNA-519c mediates endotoxin adaptation in pregnancy. Am J Obstet Gynecol 2021;225:681.e1-20.
51. Ogoyama M, Takahashi H, Suzuki H, Ohkuchi A, Fujiwara H, Takizawa T. Non-coding RNAs and prediction of preeclampsia in the first trimester of pregnancy. Cells 2022;11:2428.
52. Zhao Z, Moley KH, Gronowski AM. Diagnostic potential for miRNAs as biomarkers for pregnancy-specific diseases. Clin Biochem 2013;46:953-60.
53. Oskovi Kaplan ZA, Ozgu-Erdinc AS. Prediction of preterm birth: Maternal characteristics, ultrasound markers, and biomarkers: An updated overview. J Pregnancy 2018;2018:8367571. eCollection 2018.
54. Wikström T, Kim SH, Leverin AL, Wennerholm UB, Jacobsson B, Valentin L, *et al*. Association between miRNAs in serum at 10-14 gestational weeks and spontaneous preterm delivery. Acta Obstet Gynecol Scand 2024;103:2013-23.
55. Weiner CP, Dong Y, Zhou H, Cuckle H, Ramsey R, Egerman R, *et al*. Early pregnancy prediction of spontaneous preterm birth before 32 completed weeks of pregnancy using plasma RNA: Transcriptome discovery and initial validation of an RNA panel of markers. BJOG 2021;128:1870-80.
56. Carbone IF, Conforti A, Picarelli S, Morano D, Alviggi C, Farina A. Circulating nucleic acids in maternal plasma and serum in pregnancy complications: Are they really useful in clinical practice? A systematic review. Mol Diagn Ther 2020;24:409-31.
57. Whitehead CL, Teh WT, Walker SP, Leung C, Larmour L, Tong S. Circulating MicroRNAs in maternal blood as potential biomarkers for fetal hypoxia *in-utero*. PLoS One 2013;8:e78487.
58. Ramzan F, Rong J, Roberts CT, O'Sullivan JM, Perry JK, Taylor R, *et al*. Maternal plasma miRNAs as early biomarkers of moderate-to-late-preterm birth. Int J Mol Sci 2024;25:9536.
59. Gál L, Fóthi Á, Orosz G, Nagy S, Than NG, Orbán TI. Exosomal small RNA profiling in first-trimester maternal blood explores early molecular pathways of preterm preeclampsia. Front Immunol 2024;15:1321191. eCollection 2024.
60. Chen J, Liu T, Cui H, Na Q, Liu S. MiRNA-26a-5p inhibits preterm labor initiation by targeting and regulating TRPC3 ion channel protein expression. Environ Toxicol 2024;39:357-66.
61. Ray A, Pradhan D, Arora R, Siraj F, Rastogi S. Microarray profiling of serum micro-RNAs in women with Chlamydia trachomatis-associated recurrent spontaneous abortion: A case control study. Microb Pathog 2023;182:106273.
62. Freiría-Martínez L, Iglesias-Martínez-Almeida M, Rodríguez-Jamardo C, Rivera-Baltanás T, Comís-Tuche M, Rodrígues-Amorím D, *et al.* Human breast milk microRNAs, potential players in the regulation of nervous system. Nutrients 2023;15:3284.
63. Gupta JK, Care A, Goodfellow L, Alfirevic Z, Müller-Myhsok B, Alfirevic A. Genome and transcriptome profiling of spontaneous preterm birth phenotypes. Sci Rep 2022;12:1003.
64. Wang Y, Tang Y, Yang X, Xu J, Chen Y, Xu J, *et al.* Immune dysfunction mediated by the ceRNA regulatory network in human placenta tissue of intrahepatic cholestasis pregnancy. Front Immunol 2022;13:883971.
65. Mavreli D, Theodora M, Avgeris M, Papantoniou N, Antsaklis P, Daskalakis G, *et al*. First trimester maternal plasma aberrant miRNA expression associated with spontaneous preterm birth. Int J Mol Sci 2022;23:4972.
66. Zhou D, Xu X, Liu Y, Liu H, Cheng X, Gu Y, *et al.* MiR-195-5p facilitates the proliferation, migration, and invasion of human trophoblast cells by targeting FGF2. J Obstet Gynaecol Res 2022;48:2122-33.