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Biosensing Technologies for Enhanced Maternal-Fetal Care: A Comprehensive Overview

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ABSTRACT: This paper presents an extensive review of recent advancements in biosensor technology tailored for maternal and fetal care during pregnancy. It examines key applications, including fetal Down's syndrome detection, hormonal imbalance monitoring in the first trimester, wireless monitoring in neonatal and pediatric ICUs, and skin interfaced biosensors for tracking maternal health. Detailed discussions encompass the use of surface plasmon resonance (SPR) biosensors and electrochemical detection methods for precise diagnosis. Additionally, it investigates the development of modular, battery-free platforms for continuous monitoring in critical care settings and for remote maternal health monitoring. Addressing relevant challenges such as accuracy, biocompatibility, and data management, the paper underscores the potential of biosensors to transform maternal care through real-time monitoring and personalized interventions.

KEYWORDS: Biosensor, maternal, fetal, nanomaterials, neonatal

I. INTRODUCTION

Maternal-fetal health is an essential area of reproductive medicine that includes the physiological, biochemical, and psychological aspects of pregnancy. It encompasses the delicate interplay of maternal and fetal systems, with the goal of improving outcomes for both mother and child. From preconception care to postpartum follow-up, ensuring maternal-fetal health is critical in lowering the risk of negative pregnancy outcomes and enhancing the well-being of both individuals.

Biosensing technologies have become a critical element in this case, where their use has profoundly altered prenatal monitoring and intervention techniques. A biosensor is a self-contained integrated receptor-transducer device, which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element [1]. A biosensor usually has three important components: the analyte of interest, the bioreceptor element that identifies a specific analyte, and the transducer element, which gives a measurable chemical, optical, or electrical signal.

These novel instruments provide an integrated approach to monitoring mother and fetal well-being, delivering real-time data on vital signs, biomarkers, and physiological factors that are critical for a healthy pregnancy. Biosensors enable healthcare practitioners to discover anomalies early, customize treatment regimens, and reduce possible hazards to maternal and fetal health by utilizing modern sensor technology and sophisticated data processing tools.

In this study, we look at the many biosensing technologies used in maternal-fetal care, including their working principle, construction, clinical uses, strengths, and limitations. Through this review, we hope to highlight a variety of biosensors for optimizing prenatal care practices and improving mother and fetal outcomes.

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II. TYPES

2.1. Growth Restriction biosensors:

Fetal Growth Restriction (FGR) is associated with more than half of all still-births as well as long-term health with increased risk of cardiovascular disease for survivors. Fetal Growth Restriction (FGR) is a prevalent condition where a fetus fails to achieve its genetically determined potential size. One study used mini-microphones near uterine arteries to capture vascular sounds, aiding Fetal Growth Restriction (FGR) detection. Turbulent blood flow, indicative of arterial murmurs, was identified in 3.1% of tests, correlating with ultrasound Estimated Fetal Weight (EFW) differences. Biosensor results significantly correlated with EFWs during weeks 37–39, highlighting the biosensor's role in early FGR detection and monitoring, potentially improving pregnancy outcomes [1]. Biosensors integrated into lab-on-a-chip systems play a vital role in detecting and monitoring FGR. Impedance spectroscopy and Transepithelial electrical resistance (TEER) measurements assess placental barrier health, detecting changes in placental cell barrier function and disruptions in tight junctions crucial for nutrient and oxygen delivery to the fetus, contributing to FGR [2]. In a study investigating the impact of nanoparticles on placental barrier function, biosensors revealed acute cytotoxicity and disruptions in placental integrity, potentially contributing to FGR [2]. In one study [3], researchers focused on insulin-like growth factor binding protein-1 (IGFBP-1), a biomarker associated with FGR. Utilizing free-flow electrophoresis (FFE) and BIAcore biosensor analysis, they assessed Insulin-like Growth Factor-binding Protein 1 (IGFBP-1) phosphoisoforms and their interaction with insulin-like growth factor-I (IGF-I). Elevated IGFBP-1 levels were noted in FGR, with biosensor analysis playing a crucial role in assessing IGFBP-1's interaction with IGF-I, providing insights into FGR diagnosis and management. Another investigation [4], delved into the effects of hypoxia and nutrient deprivation on IGFBP-1 phosphorylation and its impact on inhibiting IGF actions. Cellular experiments revealed approximately 2- to 2.5-fold higher IGFBP-1 levels in conditions of hypoxia and leucine deprivation compared to controls. Surface plasmon resonance (SPR) analysis using a Biacore X instrument elucidated the interaction between IGF-I and IGFBP-1, highlighting the influence of phosphorylation on IGFBP-1's ligand binding kinetics. This study provided valuable insights into the molecular mechanisms underlying FGR. Furthermore, an investigation [5] into the angiomodulatory imbalance observed in pregnancies with features of pre-eclampsia or FGR emphasized the importance of understanding placental vascular pathology in these conditions. Alterations in placental vessels, syncytial pathology, and nutrient transport efficiency contribute to FGR. Understanding these mechanisms is crucial for building a biosensor. Elevated serum Human chorionic gonadotropin (hCG) levels are associated with intrauterine growth restriction (IUGR). Researchers developed a graphene oxide-peptide-based surface plasmon resonance (SPR) biosensor for sensitive detection of hCG in pregnancy disorders, enhancing specificity and sensitivity through modified peptide aptamers and microfluidic strategies [6]. Achondroplasia, a skeletal dysplasia leading to intrauterine growth restriction, is associated with FGFR3 mutations. A non-invasive electrochemical DNA biosensor with high sensitivity and selectivity was developed for detecting FGFR3 mutations, offering convenience for prenatal diagnosis and patient care. This biosensor utilizes a sandwich-type DNA assay and employs hemin-MOFs/PtNPs composites for signal amplification [7].

2.2. Gestational diabetes biosensor:

During pregnancy, gestational diabetes mellitus (GDM) is a type of metabolic illness characterized by hyperglycemia brought on by abnormalities in the expectant mother's insulin action, production, or both. During pregnancy, the placenta produces more hormones which affects how well insulin functions in cells and raises blood sugar levels. The newborn is affected by an increase in insulin as they grow because it counteracts hormones and raises blood sugar levels. Along with that, gestational diabetes is known to cause many organ failures, specifically the eyes, kidneys, nerve, heart, and blood vessels are often connected to chronic hyperglycemia. It is also found to increase the complications associated with birth trauma, hyperbilirubinemia, hypoglycemia, stroke, and macrosomia[8]. Because of their large surface area, biocompatibility, increased sensitivity, and selectivity, nanomaterials have recently drawn the attention of researchers working to build high-performance glucose sensors. It has been demonstrated that nanomaterials can enhance the ability of different sensors to detect glucose oxidase and hence identify gestational diabetes. The development of sensing techniques for gestational diabetes and the use of various nanomaterials in glucose monitoring during pregnancy are covered in this review[9].

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Anisotropic gold nanotriangles have also been used for this purpose. They were synthesized by a fast seedless growth process. The gold nanotriangle monodispersed colloid with high yield was obtained by a depletion induced interaction based purification process. A localized surface plasmon resonance peak of the modulated AuNTs is coherent with the Raman excitation light at 638 nm wavelength. However, the finite element computation results show the better performance of AuNT clusters using the 785nm laser source on account of a red shift in their LSPR properties and was used for the surface-enhanced Raman scattering immunoassay . To stabilize the SERS immunoassay platform, a self-assembly strategy with a thiol group and ON-OFF strategy in the heat map was conducted.The assay range of 10.15–10–6 g/mL, good reliability (R2 = 0.994, clinically relevant range), femto-scale limit of detection (3.0 × 10–16 g/mL), and excellent selectivity without interference from other biomarkers were all demonstrated by the sandwich SERS immunoassay biosensor platform for adiponectin detection. This demonstrated the potential for accurately determining the levels of adiponectin in pregnant women's biofluids. Thus, our technique has the potential to be used as a clinical biosensor capable of identifying numerous obstetric problems during early pregnancy and is the first to quantitatively detect adiponectin based on SERS technology for early identification of gestational diabetes mellitus [10].

The pathophysiology of GDM depends on microRNA-29b (miR-29b), which can be exploited as a molecular biomarker for diagnosis. The present GDM screening technologies have limitations, therefore a sensitive detection approach is desperately needed to assess serum miR-29b in GDM patients and help treat the condition. This work developed Co7Fe3–CN nanoparticles (NPs), an electrochemical biosensor. The ultra-sensitive detection and quantification of miR-29b was achieved by means of a duplex-specific nuclease (DSN) signal amplification method with a linear range of 1-104 pM and a low detection limit of 0.79 pM. The conventional qRT-PCR method was used to test the constructed biosensor's dependability and applicability. The results showed that the GDM patients' serum miR-29b content was considerably lower than that of the control group (P = 0.03). With qRT-PCR and the biosensor, in particular, miR-29b concentrations were found to range from 2.0 to 7.5 and 2.4 to 7.3 pM, respectively. These comparable outcomes suggested the possibility of using a biosensor based on miR-29b detection for GDM patient point-of-care testing in clinical settings [11].

Early-stage gestational diabetic mothers are more susceptible to hypoglycemia and hyperbilirubinemia, or jaundice. For the sake of the healthiest kid and the safest delivery, it is therefore imperative to keep an eye on the diabetes and jaundice conditions during pregnancy. However, nanotechnology has shown a quick development that can be used to get over these problems. The success of high-performance diagnosis in detecting gestational diabetes and jaundice is attributed to the use of suitable biomarkers [12].

2.3. Amniotic fluid leakage biosensors:

Fetal hydrocephalus is a condition involving excessive accumulation of intraventricular cerebrospinal fluid with ventricular dilation. It often leads to malformation or devastating neurological consequences of developing fetal brains.A new prototype ventriculo-amniotic shunt device was developed to relieve high pressure in fetal ventricles with AS. It consists of a 3 Fr neurovascular catheter as the conduit to drain excessive CSF, superelastic nitinol mesh as the anchor to prevent device dislocation and a PEUU membrane attached on distal end of the catheter tube as the passive one way valve to prevent the reflux of amniotic fluid. The device can be easily collapsed into a delivery needle. The sensing part consists of a parallel plate capacitor, i.e., a 2 μm dielectric elastomer layer sandwiched between two 300 nm magnesium layers. The sensor pattern was designed to be serpentine curves to allow for some degree in flexibility and stretchability. All the flow sensor parts were encapsulated with two 1.4 μm polyimide layers and 50 μm silicone elastomer layers for insulation. The complete encapsulation using silicone elastomer offered a great biocompatibility, while avoiding electrical leakage during measurement [13].

In one study, it was shown that the level of bilirubin in children occurs 10- times higher than that of adults (the normal level of total serum bilirubin concentration in healthy humans is in the range 0.30-1.20 mg/dl). Excess levels of bilirubin are typically related to liver infections , haemolytic conditions which are seen as a particular concern including newborns. A lot of work has been done for amperometric bilirubin biosensors based on enzymes . Generally the bilirubin biosensors are based on one enzyme, BOx. Bilirubin is oxidized in the presence of BOx to yield biliverdin and hydrogen peroxide (H2O2).

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Alternatively, conducting polymers (CP) biosensors based on bilirubin biosensors work optimally within less than 5s, pH 7, temperature 30 °C, concentration range of 0.1-50 µM with detection limit 0.04 µM and stable over a period of 60 days. They incorporate entrapping of biomolecules during electro-polymerization in a single step, furthermore uniform mounting of the exterior of substrate electrodes of thick or thin films . The conducting polymer bilirubin biosensor based on the following support has been accounted: conductive poly-terthiophene–Mn(II) complex [14].

In a study relating neonatal sepsis related biosensors, C-Reactive Protein and Procalcitonin are involved , which are acute phase reactants and are widely used in current clinical practice to detect systemic inflammation and infection. CRP is synthesized in the liver in response to proinflammatory cytokines (interleukin-1β [IL-1β], IL-6, and tumor necrosis factor [TNF]), and it is released into the systemic circulation after inflammation or infection.PCT, the prohormone of calcitonin, is limited to thyroid neuroendocrine cells, and it is not released into the systemic circulation before cleavage into calcitonin.The method of diagnosis is an IMR assayThe reagent with anti-CRP antibodies was referred to as the CRP reagent, and the reagent with anti-PCT antibodies was referred to as the PCT reagent. The mean diameters of the magnetic nanoparticles in the CRP and PCT reagents were 53.6 ± 10.6 nm and 51.0 ± 10.5 nm, respectively. The magnetic concentration of the reagent was 0.1 emu/g, which was stored at 4°C [15].

2.4. Maternal anemia biosensors:

In a study supporting maternal anemia related biosensors, electrical and electrochemical sensors were used, which enable the estimation of hematocrit and Hb level by measuring key electrical parameters including impedance, capacitance and electric current of blood constituents. StatStrip Hb/Hct developed by Nova Biomedical leverages the electrochemical method for measuring Hb level and hematocrit (Hct) using 1.6 µL of blood in 40 seconds [16].

In this study [17] , they demonstrated the possibility of using graphene to develop an FET biosensor for the detection of serum ferritin protein, whose level gives reliable information about iron deficiencies in the human body. From their analysis, the ferritin detection limit of the GFET biosensor is 5.3 ng/L (10 fM), which is the lowest detection limit reported for ferritin in the literature, while the detection range is 5.3 ng/L (10 fM) to ~0.5 µg/L (1 pM). These results show that there is excellent potential in using these GFETs for non-invasive ferritin sensing characterized by very low detection limits.

This review [18] focuses primarily on the potential of developing on-chip microfluidic systems for Iron Deficiency Anemia (IDA) detection where the cut-off level and reference range of biomarkers differ based on the age population, wherein the serum ferritin concentration for children (1 to 5 years of age) and adults is 12 ng/mL and 15 ng/mL, respectively. The membrane-based separation method was first designed as a plasma separation method that uses a matrix of hydrophilic sintered porous material. The design basically comprises an inlet and outlet, with the matrix placed between the two. When whole blood is injected into the inlet, the coagulating agent in the matrix coagulates the blood, thereby trapping the RBCs and yielding filtered plasma at the outlet. The matrix is made from hydrophilic sintered porous material and acts as a filter. The sintered material can be made from glass, steel, ceramic, or plastic. A paper used polyethylene and the pore size in the material ranged from 10 to 70 µm. Another design was demonstrated wherein two matrices were sandwiched around a filter to enhance the filtration process. The filtered plasma flows directly to the receiving cuvette.

2.5. Group B Streptococcus Infection Biosensors

Streptococcus agalactiae, also known as Group B *Streptococcus* (GBS) is a neonatal, highly infectious pathogen, which infects babies under 4 weeks old. It can cause diseases like meningitis, pneumonia, which can lead to sepsis [20]. GBS is normally a harmless bacterium; it is present in the intestines. However, in neonates, the elderly and the immunocompromised, it can cause serious infections [22]. Vertical transmission of GBS from the mother to the newborn is the main cause for GBS infection. Approximately 1-2% of these infected neonates will develop early-onset GBS sepsis, which is a major cause of neonatal mortality and morbidity [21]. Hence, GBS screening during pregnancy as well as during labor becomes extremely necessary. The gold standard for diagnosis of GBS is the bacterial culture method. It is highly specific and accurate; however, it is time consuming, involves complicated operations and offers poor sensitivity [21]. The development of biosensors for the rapid identification of GBS can combat the complications experienced when preparing bacterial cultures for identification, and can make identification and diagnosis of GBS more accessible.

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In one study, an electrochemiluminescence (ECL) biosensor was developed for the ultrasensitive and specific detection of GBS, by combining CuMn-CeO_2-PEI-luminol with MNAzyme-mediated target-recycling amplification [19]. CuMn-CeO_2 nanomaterials were prepared and then stirred with polyethyleneimine (PEI) and luminol to form CuMn-CeO_2-PEI-luminol conjugate. Signal probes (SP) were immobilized and added to form CuMn-CeO_2-PEI-luminol-SP, known as SP bioconjugates [19]. The ECL sensing platform was constructed using a glassy carbon electrode [19]. Genomic DNA was extracted from vaginal/anal samples of pregnant women to screen for prenatal or intrapartum GBS. MNAzyme mediated target-recycling was carried out by adding partzyme A, partzyme B and the target DNA, which after incubation was mixed with the SP bioconjugates. 10 µL of the resulting reaction mixture was added to the electrode surface and incubated for 30 minutes at 37 °C. In order to capture the ECL signal, the electrode was washed with PBS and investigated by the MPI-A ECL analyzer [19]. This biosensor showed ultra-sensitivity and specificity of GBS detection, as well as comparable specificity and sensitivity with fluorescent PCR assay for GBS screening in clinical sample analysis, hence showing practical application potential in clinical diagnosis [19].

In another study, a molecular technique called multiple cross displacement amplification (MCDA) was used instead of other nucleic acid amplification methods like qPCR and Loop Mediated Isothermal Amplification (LAMP) due to its higher specificity [20]. A nanoparticle-based Lateral Flow Biosensor (LFB) for reporting the MCDA results within 2 minutes was used. The total procedure time for the MCDA-LFB assay was approximately 50 minutes, which is much less than the 25.6 hours required for qPCR method for GBS detection [20]. MCDA-LFB method exhibited high specificity and sensitivity. These advantages make it a good point-of-care testing diagnostic tool for the detection of GBS from vaginal and rectal swabs in pregnant women [20].

Another study devised an integrated microfluidic sample-to-answer system for nucleic acid-based detection of GBS directly from vaginal/anal swab samples [21]. The main functions of this system include on-chip pathogen thermal lysis, nucleic acid separation and real-time monitoring of the isothermal amplification process [21]. Results were obtained within 45 minutes, and the sensitivity, specificity and accuracy of this integrated system was found to be 95.24%, 100% and 98% respectively [21].

A biosensor consisting of phospholipids and fatty acid vesicles was devised to identify GBS in pregnant women and neonates [22]. The phospholipid and fatty acid vesicles contain high concentration, self-quenched carboxyfluorescein. This is released on lysis of the vesicle caused by virulence factors expressed by GBS, and becomes diluted and fluorescent [22]. This easy to use, low-cost biosensor takes around 45 minutes to obtain the result, with a sensitivity, specificity and accuracy of 83.3%, 85.7% and 85.3% respectively [22].

2.6. Biosensor for Fetal RhD Status Detection in Maternal Blood

Rhesus Hemolytic Disease (RHD) causes fetal hemolysis, causing high mortality and morbidity of the fetus. RHD is caused by the maternal IgG antibodies produced by RhD negative pregnant women against the RhD antigen of the fetal RBCs of the RhD positive child. Prenatal determination of the fetal RhD genotyping is useful in the management of RhD incompatibility [23]. Cell-free fetal DNA (cffDNA) from the maternal plasma or serum is generally used to perform qPCR in the non-invasive detection of fetal RhD status [23]. However, this method can be time consuming and expensive [24].

In one study, a nanopolymer coated biosensor was devised to detect fetal RhD antigens on maternal blood. Hema-Mac, a nanopolymer, was applied on the surface of Au ceramic electrode to form Au-Poly HemaMac electrode [23]. RhD antibody was then immobilized on the modified electrode surface with aniline and then trapped by immersing the electrode in a solution of a crosslinking agent for 1 hour with UV light for polymerization. The electrode was then rinsed with double distilled water and stored at 4°C for further use [23]. This biosensor is simple to construct, sensitive and specific [24]. It does not require any expensive apparatus when compared with the routine fetal RhD determination performed during early pregnancy [24]. Fetal RhD status can be determined within a few minutes using this biosensor, making it a convenient tool for detecting fetal RhD antigens present in maternal blood [23].

2.7. Biosensor for Detection of Fetal Down's Syndrome

Down's syndrome is the most common chromosomal abnormality. Advanced maternal age and late marriage have led to an increase in maternal pregnancy diseases as well as abnormal fetal diseases, with Down's syndrome being one of them. Down's syndrome can be diagnosed by prenatal screening by using DNA or serum biomarkers [25].

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Serum biomarkers used for the detection of fetal Down's syndrome include pregnancy-associated plasma protein A (PAPP-A), human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), inhibin A and unconjugated estriol (uE) [25].

In a study performed, a surface plasmon resonance (SPR) biosensor was designed to detect PAPP-A2, which is a metalloproteinase like PAPP-A, in maternal serum samples to screen for fetal Down's syndrome [25]. Carboxyl-MoS_2 nanocomposites were synthesized by adding sodium hydroxide and chloroacetic acid to the MoS2 sheet solution [25]. The sensor chip was made by using a glass substrate, on which chromium and gold thin films were deposited using thermal evaporation deposition. The carboxyl-MoS_2 nanocomposites were then added to the sensor chip. This carboxyl – MoS_2 surface was conjugated with an antibody protein of anti-PAPP-A2, and the antibodies were immobilized. This carboxyl-MoS_2 based SPR biosensor is simple and has low cost of development, and is a rapid and effective assay to detect Down's syndrome biomarkers in serum [25].

In another study, a carboxylated graphene oxide (GO)-based surface plasmon resonance biosensor was devised to detect the levels of hCG protein in maternal serum to identify fetal Down's syndrome [26]. To manufacture the biosensor, carboxylated-GO sheets were immobilized on the sensing substrate, which consisted of a gold film to form a sensing film. Biorecognition peptides were then immobilized to the carboxylated-GO surface, which can interact with hCG protein present in the serum. It was found that this carboxyl-GO-based SPR biosensors showed very high sensitivity, specificity and accuracy [26].

2.8: Biosensors for Detection of Hormonal Imbalance in the First Trimester of Pregnancy

Pregnancy hormones play an essential role in ovulation, early implantation and attachment of the embryo. In addition, normal hormonal balance is also important in maintaining pregnancies during the first trimester. The hormones, human chorionic gonadotropin (hCG), progesterone, estrogen and four of its metabolites (estradiol, estrone, estriol, estetrol), as well as relaxin play an essential role in the development of the fetus during the first trimester. Imbalances in these hormones during the first trimester have been directly linked to miscarriages[27].

One of the studies conducted a comprehensive compilation of electrochemical biosensors in the detection of hormones. Individual hormone studies were performed, such as hCG, progesterone (P4), and estradiol (E2), which show a variety of approaches. Examples include screen-printed carbon electrodes modified with gold nanoparticles for hCG detection, graphene-based electrochemical sensors for P4 monitoring, and impedimetric biosensors with immobilized antibodies for E2 measurement, all of which achieve impressive detection limits in a variety of sample matrices. These discoveries highlight the utility of electrochemical biosensors in early pregnancy surveillance for hormone-related diseases.

A paper exclusively on Progesterone-HCG detection by electrochemical sensor described in detail the biosensor, consisting of a planar strip featuring four graphite working electrodes (WEs) positioned radially around a silver pseudo-reference electrode, aimed at minimizing disadvantages associated with traditional serial arrangements of electrodes [28] To aid selective antibody immobilization, the electrode surfaces have been pre-coated with anti-rabbit IgG Fc fraction. This pre-coating layer immobilizes the capture antibodies, anti-progesterone IgG and anti-β-hCG IgG, on WEs. The construction technique involves coating the graphite WEs with 10 µL of 0.1 M carbonate buffer (CB) at pH 9.6, containing 500 µg/mL of anti-rIgG Fc, followed by washing with 20 µL of phosphate saline buffer containing Tween-20 (PBS-T). After adding 10 µL of CB solution containing 30 µg/mL of anti-progesterone IgG and 30 µg/mL of anti-β-hCG IgG to the working surface, incubate for 1 hour at room temperature. Wash with PBS-T and store at +4 ◦C for nearly a month without sensitivity degradation. For progesterone detection, a direct competitive scheme is employed, wherein the modified WEs are incubated for 300 seconds with 5 µL of 0.1 M phosphate saline buffer (PBS) containing 10% v/v methanol at pH 7.4, along with various concentrations of progesterone and progesterone labeled with alkaline phosphatase (prog-AP), were diluted 1:1000. After incubation, rinse each WE with 50 µL of 0.1 M diethanolamine buffer (DEA) at pH 9.6. After washing, the modified WE is incubated for 300 seconds with 5 µL of 0.1 M PBS buffer + 10% v/v methanol at pH 7.4, containing different concentrations of β-hCG (ranging from 0 to 1000

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IU/L), and a fixed dilution (1:500) of the secondary antibody anti-β-hCG labeled with alkaline phosphatase. The working surface is then rinsed with 50 µL of 0.1 M DEA buffer at pH 9.6. The extent of the affinity reactions is evaluated using Differential Pulse Voltammetry (DPV) with optimum parameters: range potential of 0 to +700 mV, scan rate of 70 mV/s, pulse amplitude of 70 mV, and pulse width of 50 ms. The sensor can detect progesterone and β-hCG with high sensitivity and specificity.

2.9. Skin-interfaced biosensors for wireless monitoring in neonatal and pediatric ICUs

Premature infants, weighing as little as 500g, require continuous monitoring of their vitals. But the existing technologies use multiple electrodes and interfaces attached to the skin with adhesive tapes connected by wires to electronic processing systems that are often tethered to the wall. This system of hardware often frustrates both routine and specialized procedures in clinical care. It also leads to induction of other types of complications, including thrombus formation and occlusion, infection (e.g. sepsis), rupture, pseudoaneurysm, bleeding, and death[29]. Hence, a wireless system that is non-invasive and capable of continuous monitoring is highly beneficial to enhance healthcare at neonatal and pediatric critical care units.

The study conducted gives the double component biosensor model which includes, the chest unit having a wide-bandwidth 3-axial accelerometer (BMI160, Bosch Sensortec), a clinical-grade temperature sensor (MAX30205, Maxim Integrated), and an ECG system that consists of two gold-plated electrodes. The limb unit includes an integrated pulse oximetry module (MAX30101, Maxim Integrated) for measuring dual wavelength PPGs and a temperature sensor (MAX30205, Maxim Integrated). The power management circuit for battery operation uses a voltage regulator to provide supply voltages required for the various components (3.3V or 1.8V). The modular battery-free platform includes an inductive coil tuned to 13.56 MHz, a full-wave rectifier, and a two-stage cascaded voltage regulating unit[29].

The construction of this biosensor involves a flexible, modular design with a soft, elastomeric casing enclosing a primary body that holds connected electrical components. Strong performance is ensured by its power system, which makes use of a modular primary battery with reversible magnetic coupling. Thin silicone pads are used to create electrical connections between measurement electrodes and a hydrogel interface, ensuring a completely sealed and waterproof design. Precise techniques are used in fabrication, such as soldering electrical components onto flexible printed circuit boards with laser ablation patterns. The limb unit's translucent sections hold LED modules, while the chest unit uses a gentle silicone material for encapsulation. For stable electrical connections, carbon black-polydimethylsiloxane (CB-PDMS) sheets are connected to electrode pads and gold electrodes using conductive tape. These films function as strain-isolating layers.

In addition to recording heart sounds (SCG), the high-speed 3-axis accelerometer also records heart rate, systolic interval, pre-ejection period (PEP), and left ventricular ejection time. The ECG, SCG, and temperature sampling frequencies are 504 Hz, 0.2 Hz, and 100 Hz, respectively.

The study also highlights usage of biosensors in Kangaroo Care (KC), a technique that involves a caregiver and a newborn coming into skin-to-skin contact. These measurements include heart rate (HR), blood oxygen levels (SpO2), central and peripheral skin temperatures, and activity levels. According to prior studies, skin-to-skin contact during KC caused a progressive rise in peripheral skin temperature.

Accelerometry data was used to evaluate activity levels, and the mean values during rest and KC episodes were 0.07 ± 0.02 g/s, whereas during hands-on care they were 0.24 ± 0.05 g/s. These results highlight the possibility of detecting newborn disturbance during care activities.

The accelerometer also shed light on vocal biomarkers, including the frequency of crying which can be a sign of neurophysiological conditions such pain, stress or birth trauma.

Along with skin temperature, the limb unit measures PPG (blood volume fluctuations) at red and infrared wavelengths. PPG data is captured at 100 Hz, while temperature data is sampled at 0.2 Hz.

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This biosensor can be mounted in two different ways: for premature neonates, it can be wrapped around the ankle to the base of the foot; for older babies, it can be wrapped around the foot, toe, or wrist to hand.

2.10. Biosensors for Fetal Heart Rate (FHR) Monitoring

Fetal heart rate monitoring is crucial for measuring the fetus's health during pregnancy. Changes in FHR patterns might indicate a variety of issues, including fetal distress, hypoxia, or metabolic acidosis, requiring early intervention to reduce potential dangers to the fetus. Continuous FHR monitoring during labor helps guide clinical management decisions, including the timing and style of delivery, to maximize outcomes for both the mother and the baby.

A study delved into the design and implementation of a noninvasive phonocardiographic fiber-optic sensor and its associated adaptive signal processing system for fetal heart rate (fHR) monitoring. The probe utilizes sensing elements operating on the basis of the Mach-Zehnder Interferometer. Interferometers belong to the highest-performance group of optical sensors as they are capable of measuring even tiny differences in the optical fiber length and the fiber core refractive index. These differences can be measured on the scale of the wavelength of the light source. The Mach-Zehnder interferometer is the most common configuration. The source is divided into two fiber arms forming the reference and the measurement paths. The measurement fiber is encapsulated into polydimethylsiloxane (PDMS) constructing the acoustic-sensitive probe, while the reference fiber stays in a stable environment. The output beams then recombine at a second 3 × 3 coupler terminated in photodetectors[30]. The measurements probe was encapsulated in PDMS with the designation of Sylgard 184, which is a two-component casting compound: the A component creates its own pre-polymer and the B component is a curing agent. Both components are mixed together with a weight ratio of 10:1 (A:B), Bubbles and microbubbles that result from the combination of the pre-polymer and the curing agent can be removed using an ultrasonic bath. Homogeneity of the connection is achieved by using a laboratory shaker. The measurement probe contains two connectors of FC/APC type [30]. The sensors are attached to the mother's body using 10 x 10 mm self-adhesive straps. The measurement sensor weighs 150 grams and has a diameter of 100 millimeters. Using a fiber optic sensor with two interferometric components, fetal heart rate (fHR) data are separated from maternal heart signals. Additionally, an adaptive filtering system using LMS (Least Mean Squares) and NMLS (Normalized Least Mean Squares) algorithms separates and isolates the fHR from mixed data, enabling continuous monitoring of the fetal heart rate during pregnancy.

Another paper described a monitoring system consisting of four modules: data acquisition, transmission, storage, and analysis platform. Abdominal Electrocardiography (AECG) signals are collected from pregnant women by carefully placing electrodes on their skin. The acquisition module filters and amplifies the signals, changing them from analog to digital. The transmission module transmits abdominal ECG signals to a PC via Bluetooth or stores them on a memory card. The analysis platform shows AECG waveforms and then processes and analyzes the data.
It is investigated that three linearly independent ECG electrodes can be used to construct a surface ECG vector map[31]. A buffer is designed to increase input impedance and improve load capacity and noise immunity. Simultaneously, a preprocessing circuit is added to the hardware acquisition system composed of a second-order passive low-pass filter and a limiting circuit, which plays a crucial role in eliminating high-frequency interference and overvoltage protection[31].The power line interference, baseline drift, and impulsive artifacts of the AECG are mostly reduced following the signal noise cancellation step using a notch filter. Maternal ECG (MECG) is a major component of the AECG signal and masks fetal ECG signals. Thus, it is necessary to effectively cancel the MECG signal. Blind source separation (BSS) is used to solve the problem[31].

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III. TYPES OF BIOSENSORS

Biosensor	Working Principle	Detection Method	Applications	Strengths	Limitations	Reference
Growth Restriction Biosensor	Biological interfaces with sensors.	electrochemical detection, surface plasmon resonance (SPR), impedance spectroscopy, and free-flow electrophoresis (FFE).	FGR, IUGR, and placental dysfunction.	sensitive, selective, and real-time detection	optimization for commercial scalability is not there.	[1-7]
ational diabetes biosensor	Surface plasmon resonance	Raman spectroscopy, immunoassay	Detection of diabetes in mother and fetus	Suitable, reliable	Risky, less cost effectiveness	[8-12]
Amniotic fluid Biosensor	Biological interfaces with sensors.	polarography , fluorometry , enzymatic assay,capillary electrophoresis and diazo reaction,	Monitoring of Cerebrospinal Fluid, hepatological disorders, preterm birth, and Early-Onset Neonatal Sepsis	Suitable, effective and reliable	Not non invasive	[13-15]
Maternal anemia Biosensor	Biological interfaces and techniques with sensors.	Hematology analyzer, Enzyme Immobilisation, Surface plasmon resonance, microfluidics	Anemia detection in gestating mothers	Suitable, effective and reliable	Not non invasive	[16-18]
Group B *Streptococcus* Infection Biosensors	Biological interfaces and techniques	Electrochemiluminescence, lateral flow, microfluidics	Detection of group B *Streptococcus* in pregnant women	Suitable, effective and reliable	Low specificity and sensitivity in the presence of less quantity of	[19-22]

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	with sensors				bacteria	
Biosensor for Fetal RhD Status Detection in Maternal Blood	Biological interfaces and techniques with sensors	Nanopolymer coated, immunospecificity	To check for Rhesus hemolytic disease	Suitable and reliable	Chance of false positives/negatives	[23-24]
Biosensor for Detection of Fetal Down's Syndrome	Biological interfaces and techniques with sensors	Surface plasmon resonance	To check for the presence of biomarkers indicating fetal Down's syndrome	Suitable and effective	Hard to detect small quantities of biomarker	[25-26]
Biosensors for Detection of Hormone Imbalance in the First Trimester of Pregnancy	Biological interfaces and techniques with sensors	Electrochemical	Detection of hormonal imbalance - HCG, Estrogen, Progesterone.	High sensitivity and selectivity, fast detection	Prone to interference from the sample matrix, may require rigorous calibration.	[27-28]
Skin-interfaced biosensors in NICUs and PICUs	Biological interfaces and techniques, integration of multiple sensors	Accelerometry, ECG, pulse oximetry, temperature sensing	Monitoring heart rate, blood oxygen levels, skin temperatures, and activity levels. Kangaroo Care (KC).	Flexible, soft, waterproof casing. Precise fabrication, stable performance.	Loss of accuracy in detecting specific vocal biomarkers and distinguishing between care activities.	[29]

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Biosensors for Monitoring Fetal Heart Rate	Biological interfaces and techniques, integration of multiple sensors	Mach-Zehnder Interferometer for fetal heart rate (fHR) monitoring and abdominal electrocardiography (AECG) for maternal heart rate and fetal heart activity monitoring	Continuous monitoring of fetal heart rate during pregnancy and real-time assessment of maternal and fetal cardiac activity.	Non-invasive, accurate monitoring, wireless transmission, real-time assessment.	Requires skilled application and setup; may involve complex signal processing; potential for interference and artifacts.	[30-31]

V. CHALLENGES AND FUTURE DIRECTION

Biosensors offer tremendous potential for enhancing maternal care, but they also come with their own set of challenges:

1. Accuracy and Reliability: Ensuring the accuracy and reliability of biosensor readings is crucial, especially in maternal care where the health of both the mother and the fetus is at stake. Variability in readings due to environmental factors, user error, or device malfunction can lead to inaccurate interpretations and potentially harmful decisions.

2. Biocompatibility: Biosensors used in maternal care must be biocompatible to prevent adverse reactions when in contact with maternal tissues or fluids. This is particularly important for continuous monitoring applications where the sensor may be in direct contact with the skin or blood for extended periods.

3. Sensitivity and Specificity: Biosensors need to be sensitive enough to detect relevant biomarkers or physiological parameters at low concentrations or in small sample volumes. At the same time, they should be specific enough to distinguish between similar molecules or signals that may be present in maternal fluids.

4. Miniaturization and Portability: Maternal care often requires monitoring both in clinical settings and at home. Biosensors need to be miniaturized and portable to enable convenient use outside of the hospital or clinic environment, while still maintaining high performance.

5. Data Management and Interpretation: Biosensors generate large amounts of data that need to be managed, analyzed, and interpreted effectively. Ensuring seamless integration with electronic health records (EHRs) and providing user-friendly interfaces for healthcare providers and patients are essential for translating raw sensor data into actionable insights.

6. Long-Term Stability: For continuous monitoring applications, biosensors must maintain their performance and calibration over extended periods to provide reliable data over the entire course of pregnancy and beyond.

7. Cost and Accessibility: Cost-effective biosensor solutions are necessary to ensure accessibility to maternal care across diverse socio-economic backgrounds. This includes not only the initial cost of the biosensor device but also considerations for maintenance, consumables, and associated infrastructure.

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Addressing these challenges requires interdisciplinary collaboration between engineers, material scientists, clinicians, and healthcare professionals to develop innovative biosensing technologies tailored specifically for maternal care applications.

Biosensors, as opposed to conventional diagnostic techniques, allow for ongoing monitoring of maternal and fetal parameters, giving medical professionals access to data in real time. The implementation of individualized treatment programs and the early detection of problems can both benefit from this ongoing monitoring.The incorporation of biosensors into wearable technology and mobile health technologies opens the possibility of remotely monitoring maternal-fetal parameters. This makes it possible for expectant mothers to keep an eye on their health from the comfort of their homes and makes telemedicine discussions with medical specialists possible—especially in remote or underprivileged locations.

VI. CONCLUSION

Biosensors hold tremendous promise in transforming maternal and fetal health care by offering rapid and accurate monitoring solutions that are crucial for early diagnosis and management of certain conditions like preeclampsia, gestational diabetes and group B *Streptococcus* infection. By integrating biosensors into regular healthcare practices, it becomes possible to continuously monitor vital parameters, thereby reducing the reliance on periodic testing that may miss critical changes in the mother's or fetal condition. This technology has the potential to enable remote monitoring, ensuring that pregnant women receive timely and adequate medical attention regardless of their geographic location. In conclusion, biosensors in maternal-fetal health care can provide more personalized and accessible treatment for women all around the world.

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Competing Interests
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Authors' Contributions
All the authors have contributed to the study's conception, read, and approved the final manuscript.

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