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Saving babies and families from preventable harm: a review of the current state of fetoplacental monitoring and emerging opportunities

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Neonatal outcomes have improved over the last decade following significant thrust in this area, but stillbirth, preterm birth and neonatal brain injury remain acute global problems with long-lasting parental and family psychological trauma. In 2020, 1 in every 225 pregnancies in UK ended in stillbirth, with 2 million stillbirths reported worldwide. Over 40% of all stillbirths occur during labor—a loss that could be avoided with improved fetal monitoring and timely access to emergency obstetric care when required. Nearly one-fourth of global neonatal mortality relates to intrapartum-related events. Currently, available monitoring tools rely on surrogate markers such as serial fetal size measurement, doppler assessment of fetoplacental perfusion, fetal heart rate variability, fetal movements and maternal circulating placental proteins to identify the vulnerable fetus. Continuous cardiotocography (CTG) is the current standard of monitoring for fetal assessment in labor, but a Cochrane review indicated that it failed to significantly reduce poor outcomes in newborn infants, and resulted in an increase in the number of Caesarean sections. There is an urgent need for the development of a monitoring platform to directly measure acute or chronic changes related to fetoplacental compromise which can be operated with ease both in the hospital and remotely in the home environment in high-risk pregnancies. In recent years, there has been some promising development to identify compromised fetuses using advanced technologies and artificial intelligence-based approaches. We present here the current state of fetoplacental monitoring, focussing primarily on antepartum monitoring and discuss a possible way forward using digital biomarkers in this area to protect babies and mothers in future.

Continuous risk assessment of maternal and fetal well-being is the essence of antenatal care. Deviation from the trajectory of normal physiological changes during this critical period is associated with poor outcomes e.g., stillbirth, preterm birth, as well as fetal and neonatal brain injury and long-term neurodevelopmental disabilities[1]. Only a few antenatal interventions have been shown to improve the course of fetal growth in-utero[2]. Instead, obstetricians are faced with the challenges of deciding the necessity and timing of delivery, in a manner which mitigates the risk of stillbirth and hypoxic brain injury, whilst balancing the potential consequences and related risks of iatrogenic prematurity[3,4]. Obstetric decisions and their outcomes depend on the reliability and accuracy of fetoplacental monitoring and access to high-quality emergency obstetric and neonatal care.

Despite advances in maternity care, stillbirth rates continue to be a significant global concern. Although there has been some progress in high-income countries (HIC) in reducing stillbirth, the UK stillbirth rate (SBR) has now plateaued at around 4 per 1000 births, which is higher than most

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European countries (20 of which have an SBR under 2.5)[5]. The UK National Health Service (NHS) set an ambitious target to reduce stillbirth rates and hypoxic brain injury by 50% by 2025, and introduced the 'Saving Babies' Lives' care bundle, which highlighted key evidence-based practice points to improve outcomes[6].

Stillbirth not only remains difficult to prevent but also affects some communities disproportionally. Stillbirth rates in Black and Asian women in the UK remain four times higher than in their white counterparts[6]. This has also been noted in other comparable high-income countries (HIC), such as the United States and Australia[7,8]. Low-and-middle income countries (LMICs) (particularly in sub-Saharan Africa and South-East Asia) have the highest rates of stillbirth, highlighting that this remains a major global health concern[9].The World Health Organisation's (WHO) 'Every Newborn Action Plan' set targets to reduce preventable stillbirth and disability, aiming to reduce every country's SBR to under 10 by 2035. In 2021, Guinea-Bissau reported the highest SBR of 31.21, with India reporting the highest number of stillbirths, whilst Monaco had the lowest SBR[9]. Although there are different barriers to maternity care between HICs and LMICs, similar themes transcend the country of origin and demonstrate the need for improvements in fetoplacental monitoring translatable to both HICs and LMICs.

The precise mechanisms leading to fetal injury and demise remain largely obscure. What is obvious, however, is the wider harm caused every time a baby is adversely affected or dies. Stillbirth and other adverse perinatal outcomes are deeply traumatic for both families and healthcare workers, with potential long-lasting psychological sequelae, and a significant economic burden on society. This is illustrated well by the cost of obstetric litigation claims highlighted in the recent 2022/23 NHS Resolution report which found that while obstetric claims accounted for only 13.1% of clinical claims reported, they accounted for 64% of all clinical claims by value received in that year with 41% of the total clinical negligence payments (£2.6 billion) for 2022/23 related to maternity, much of it due to obstetric cerebral palsy and brain damage claims[10]. 40% of global stillbirths still occur in labor, the majority of which are thought to be preventable[9].

Unfortunately, currently available tools for fetoplacental monitoring in clinical practice have significant limitations. To end preventable harm, there is a critical need to develop more accurate and nuanced forms of fetoplacental monitoring, to detect acute and chronic changes during the antenatal period related to fetoplacental compromise, without increasing the need for unnecessary intervention. It is important to acknowledge that the physiological dynamics observed during the intrapartum period differ from those encountered in the antenatal period. Despite a shared clinical objective aimed at minimising harm, the specific clinical questions and indicators used to identify fetal distress intrapartum differ from those applied antenatally.

Healthcare is currently in the midst of a wave of digital innovation with the potential to significantly improve the efficiency and accuracy of diagnostic and therapeutic provisions across a wide range of different clinical specialities. Particularly, with rapid advancements in machine learning and the use of artificial intelligence, there is a unique opportunity to develop automated and scalable tools with capabilities to offer remote monitoring. We present here a critical review of different fetoplacental monitoring tools currently available and explore emerging digital technologies on the horizon.

Current monitoring tools

Blood biomarkers

Serum placental growth factor (PlGF) testing in women with suspected preterm pre-eclampsia after 20 weeks of gestation has recently been recommended by the National Institute for Health and Care Excellence (NICE) in the UK[11]. The fundamental pathophysiology of pre-eclampsia lies in abnormal placental vasculature (starting with the deficient invasion of the spiral arteries by extravillous trophoblasts, a process required for adequate placentation) leading to placental dysfunction[12] and increased levels of soluble fms-like tyrosine kinase 1 (sFlt1) and decreased levels of placental growth factor (PlGF)[13]. An sFlt1:PlGF ratio of >38 has a reasonable predictive value of 36% for developing pre-eclampsia within 4 weeks[14]. However, a biomarker which could identify women at high risk of pre-eclampsia earlier in the pregnancy could provide an opportunity to offer low-dose aspirin prophylaxis, which reduces the risk of pre-eclampsia and subsequent neonatal morbidity[15,16]. Starting aspirin after 16 weeks has not been demonstrated to reduce the risk of pre-eclampsia as effectively[17]. The ASPRE trial confirmed that using a previously developed algorithm combining the current NICE screening questions, mean arterial blood pressure, uterine artery dopplers and serum concentrations of PAPP-A and PlGF at 11–13 weeks gestation could significantly increase the detection of preterm pre-eclampsia[18].

Fetal heart rate monitoring

Cardiotocography (CTG) is the standard tool for electronic fetal monitoring in the antenatal and intrapartum periods. CTG evaluates both fetal heart rate (FHR) and uterine contractions, to identify changes in FHR which could indicate fetal hypoxia and the potential need for expedited delivery. With the onset of acute hypoxia, FHR soon falls to about half the normal rate. If the hypoxia continues, this bradycardia is maintained for some time using anaerobic respiration before a terminal fall occurs if there is no timely intervention and effective resuscitation. The Dawes-Redman computerised CTG monitoring software calculates the 'short-term variability' (STV) of FHR and is a reliable predictor of fetal hypoxemia and acidaemia[19,20]. It is validated for use in the antenatal period, in the absence of uterine contractions. Fetal well-being is established if all of the system's criteria for a normal CTG are met within 60 min of monitoring, however, a holistic assessment of the patient is required to avoid overreliance on CTG analysis if subtle changes in risk occur.

The application and interpretation of intrapartum CTG however, presents separate challenges and considerations[21,22]. A 2016 Cochrane review of 12 trials involving 37,000 women noted that the use of continuous CTG in labor did not reduce the overall perinatal death rate or incidence of cerebral palsy, but did half the rate of neonatal seizures compared to intermittent auscultation. They also reported increased rates of cesarean section and operative vaginal delivery, when compared with intermittent auscultation. The INFANT trial also found that the use of the INFANT decision support software (a computerised CTG interpretation system) during intrapartum monitoring, designed to mimic the interpretation and decision-making of expert clinicians, did not improve neonatal, maternal or infant neurodevelopmental outcomes[23].

Hypoxic changes in CTG throughout a long labor may be subtle and difficult to identify, particularly when care is provided by multiple practitioners who changeover between shifts. For example, a baseline FHR in the normal range may be identified as normal, but when compared with a previously lower baseline at the start of labor, could be an important change in fetal wellbeing. The Royal College of Obstetricians and Gynecologists (RCOG) in the UK has recently launched a quality improvement programme (Each Baby Counts) to reduce the number of babies who die or are left severely disabled as a result of incidents occurring during term labor[24]. 508 cases were identified in 2020 where differences in care may have changed the final outcome, and in 29% of these cases, CTG misinterpretation was identified.

Fetal ECG monitoring (ST waveform analysis) has also been applied in labor to detect intrapartum fetal hypoxia, but with limited success[21,22].

Despite its limitations, in the absence of any other effective form of intrapartum fetal monitoring, CTG remains the universal monitoring modality. However, ongoing work using machine learning on both the intrapartum CTG and ECG might lead to a more reliable assessment of fetal well-being in the future[25].

Fetal growth charts

An integral part of antenatal care is to monitor fetal growth (either by symphysis-fundal height (SFH) or estimated fetal weight on USS) on a growth chart, in order to determine whether the rate of growth is consistent

and within a determined 'normal range'. There are several growth chart options, but the choice of the chart can influence ongoing surveillance and management of the pregnancy due to their inherent differences in growth curves. Wide variation in fetal growth among different countries, racial and ethnic groups are well established.

The most commonly used population growth charts include the Hadlock, WHO and INTERGROWTH-21st charts. The Growth Assessment Protocol (GAP) programme uses gestation-related optimal weight (GROW) customised charts, alongside a schedule of antenatal risk assessment for small for gestational age (SGA), management protocols for suspected SGA fetuses, audit tools and training. These charts incorporate maternal demographics which are thought to influence fetal growth; age, BMI, parity and ethnicity. However, the DeSIGN trial found that implementation of GAP GROW did not reduce the incidence of SGA babies when compared with standard care[26]. The INTERGROWTH-21st project aimed to develop international growth standards by assessing fetal growth in eight different countries[27]. Their analysis found that fetal growth was remarkably similar across these populations in different geographical locations when nutritional and socioeconomic needs were met, and no major genetic variation was indicated[28,29]. A 2014 Cochrane review indicated that currently there is no randomised control trial evidence to study the use of customised growth charts to detect SGA fetuses[30].

In addition to population and customised growth charts, national growth charts have also been studied. A population study of 15 European countries found that using national growth charts identified more SGA and LGA infants than using international charts and that there was a marked variation between countries[31]. Using national charts may account for anthropological and social differences within countries, however, it is also important to understand the differing levels of heterogeneity in specific countries. In this study, France has the highest level of immigration and therefore represents a diverse population of women from different ethnic and social backgrounds[32]. France also had one of the lowest differences in SGA detection when compared to international growth charts, further reflecting the potential importance of population heterogeneity when considering choice of growth chart and whether national charts are appropriate in these populations.

Fetal growth can be more accurately assessed with ultrasound than uterine palpation alone[33]. Although some SGA babies may be constitutionally small, in cases where there are true fetal growth restriction (FGR), factors such as placental insufficiency impede the fetal potential to reach its genetically determined weight. It can be difficult to differentiate a constitutionally small baby from a growth-restricted one using a single ultrasound alone. As the risk of stillbirth increases sevenfold in an SGA baby, accurate growth surveillance throughout the pregnancy is essential where growth concerns are identified[34]. There are, however, limitations for using ultrasound alone for surveillance. Measurements with fetal ultrasound are operator-dependent with well-recognised significant inter and intra-observer variability[35]. Margins of error could potentially lead to unnecessary obstetric intervention or failure to detect growth restriction. Unblinded measurements can introduce bias towards the mean, normalising relatively small yet potentially significant deviations from normal growth curves. High BMI reduces the accuracy and quality of ultrasound measurements[36], which compounded with the effect of obesity itself on fetal growth represents a high-risk demographic factor for undetected FGR, and potentially fetal demise.

A universal third-trimester ultrasound may increase the detection of SGA by threefold, and identify FGR which could lead to subsequent neonatal morbidity, whilst substantially increasing obstetric intervention[37]. A recent systematic review and cost-effectiveness analysis of universal late pregnancy ultrasound however found that assessment of fetal biometry was borderline cost-effective[38]. Implementation of such universal scanning would be highly dependent on resource availability, increase the burden on the health service, and is unlikely to be scalable to low and middle-income countries (LMIC).

Fetal Doppler examination

Umbilical artery (UA) Doppler measurement[39]. It is currently the main risk assessment tool for fetal well-being in growth restriction and is often one of the first detected abnormalities[39]. A Cochrane review found that in high-risk populations, UA Doppler measurement in risk assessment can reduce perinatal death by 34% with an associated reduction in Caesarean section and induction of labor[40]. However, a reduction in perinatal death in low-risk pregnancies has not been similarly demonstrated[41,42]. With raised UA Doppler resistance indices before 37 weeks' gestation, urgent delivery is often only indicated if there are changes in FHR. However, if a growth-restricted fetus with abnormal UA Doppler starts to demonstrate abnormal FHR patterns on CTG, particularly reduced HR variability, 77% of them will already be hypoxic[43] and potentially also have irreversible brain injury[43].

In early preterm FGR, abnormal ductus venosus (DV) Doppler are an indication of cardiac compromise and are better predictors of fetal compromise than UA or middle cerebral artery (MCA) doppler examination alone[39]. Abnormalities in DV waveforms may occur later in the chronology of FGR and are an indication for urgent delivery.

The TRUFFLE study did not reveal any difference in survival without cerebral palsy or neurosensory impairment or 2-year neurodevelopment outcome using management based on either STV (on computerised CTG) or ductus venosus (DV) Dopplers[20] in growth-restricted fetuses (EFW <10th centile with raised UA Dopplers)[20]. However, in surviving infants, there was a reduction in neurological deficit at 2 years of age in those randomised to deliver based on DV Dopplers[44]. Interestingly, in several cases of preterm FGR with subsequent fetal demise, the last DV measurements were normal and therefore it is hypothesised that in some cases, the normally expected sequelae of organ dysfunction are different, with cardiac dysfunction occurring before cerebral dysfunction[44]. These findings support the use of DV monitoring to time delivery in high-risk cases. However, this requires significant operator experience and easy access to ultrasound and is not a practical strategy in many settings.

Fetal movements

Maternal perception of fetal movements is one of the only clinical signs of fetal compromise that a pregnant woman can monitor herself. Diurnal variations in fetal movements reflect normal fetal physiology and neurological function[45]. Fetal movements have a distinct maturational character with the quantity and strength of movements steadily increasing and remaining regular from 28 weeks onwards. In intrauterine hypoxia, there is a reduction in fetal movements (RFM) likely as an attempt by the fetus to conserve energy[46]. 25% of women reporting reduced fetal movements will suffer from adverse perinatal outcomes. Although reduced fetal movements have been reported in up to half of all stillbirths, it is a difficult metric for patients to measure and can often cause great anxiety, sometimes with repeated attendances to maternity units and may result in unnecessary obstetric intervention[47]. Chronic uteroplacental insufficiency has been reported as the most common denominator of reduced fetal movement[46].

RFM can be highly non-specific and as such, clear guidance on the quantification of the minimum number of fetal movements has not yet been developed. The evidence for the implications of reduced fetal movements and outcomes is well understood, however, the evidence for the effectiveness of increased awareness on subsequent outcomes is not. The AFFIRM cluster-randomised trial, in which a care package to increase awareness of RFM in patients and clinicians was implemented, failed to reduce stillbirth[47]. Similarly, a Cochrane review concluded that there was currently insufficient evidence to suggest a method of fetal movement counting which was effective at reducing stillbirth[48]. In high-risk patients, a continuous mode of monitoring fetal movements would be beneficial, particularly in those who present with multiple episodes of reduced fetal movements (with normal ultrasound findings and normal CTG).

Methods of achieving this have been explored with the development of wearable fetal movement monitors[49,50]. Different types of sensors, including accelerometers, have been trialed and although they are able to monitor movements continuously in out-of-hospital settings, they are still less

sensitive than ultrasound and face difficulty discriminating between maternal and fetal movement. Lai et al trialed a monitor which combined both an accelerometer and an acoustic sensor and found this to be sensitive to fetal movements and able to distinguish these from maternal movements, however, noise artefacts remain a significant issue[51]. This represents a promising advance towards the development of an unmet need, a wearable fetal movement monitoring device.

Strengths and limitations of currently available monitoring tools are presented in Table 1.

Recent developments and promising options

Circulating RNA/DNA

The placenta, like many other organs, releases mRNA and miRNA into the maternal circulation, which can be analysed for placental gene expression linking with respective pathologies[52]. This could allow for non-invasive screening for pregnancy complications earlier in their pathogenesis with an opportunity for prevention, rather than solely on detection. Analysis of circulating cell-free fetal DNA is already in clinical use to detect common aneuploidies and single gene disorders, however, testing of circulating mRNA is still in development. One of the best predictive mRNA markers correlating with placental dysfunction and in-utero fetal acidaemia is endothelial membrane protein 1 (EMP1), which has been shown to have a high potential to predict severe placental insufficiency and a very high risk of stillbirth in prospective cohorts with early and late-onset FGR[53].

There have been recent advances in using maternal serum concentrations of circulating DNA and RNA to predict the risk of pre-eclampsia (and therefore potential subsequent placental dysfunction), including the ability to determine the cell type of origin of cell-free RNA (cfRNA)[54]. A study of 175 women identified 18 genes measured early in pregnancy (5–16 weeks' gestation) which were predictive of pre-eclampsia risk, and in some cases were predictive of symptom severity[55].

This represents an exciting potential for the development of an accurate non-invasive predictive biomarker for pre-eclampsia, with applications for real-time monitoring of related organ dysfunction, as cfRNA markers were altered in at least five organ systems in the context of pre-eclampsia[55]. Furthermore, cfRNA has been found to be altered in patients who deliver pre-term and accurate at predicting gestational age, therefore further studies are required to investigate the potential use of these markers as a predictive tool for pre-term birth[56].

1st trimester ultrasound

Low placental volume (PlaV), measured in the first trimester using 3D ultrasound, has been shown to be associated with FGR, SGA and pre-eclampsia[57,58]. The predictive value of PlaV is independent of other biomarkers for SGA (such as PAPP-A and maternal characteristics), however when combined, these further improve the predictive accuracy for SGA detection from 18 to 35%[59].

As abnormal haemodynamics of the spiral arteries at the uteroplacental interface (UPI) in the first trimester are the hallmark of FGR and pre-eclampsia, the utility of 3D power Doppler (PD) ultrasound to measure the degree of tissue vascularity has been investigated. This is done by measuring fractional moving blood volume (FMBV). Collins et al. have developed a software tool to calculate FMBV in 3D (3D FMBV) to create a standardised measurement of vascularity across the entire UPI[60]. They found 1st trimester FMBV to be significantly decreased in patients who developed pre-eclampsia, but no significant difference in normotensive SGA babies. Therefore, the destiny of placental function can be identified using first-trimester ultrasound, whereby pre-eclamptic pregnancies have both reduced placental vascularity and volume, but normotensive term SGA pregnancies have normal placental vascularity and reduced placental volume.

Deep Learning with 1st trimester ultrasound

Delineation of the placental borders using 3D ultrasound in the first trimester can be challenging and operator-dependent, therefore semi and fully-automated methods have been explored. Even the use of automation currently requires significant clinical input. In order for these tools to be clinically feasible, they need to be easily reproducible and ideally automated. Deep learning methods using convolutional neural networks (CNNs) require a large 'ground data set', which can be challenging to obtain for placental segmentation due to the high heterogeneity of placental locations and ultrasound images.

Table 1 | Currently available fetoplacental monitoring tools with strengths and limitations

Fetoplacental monitoring tools	Advantages	Limitations
sFLT1:PLGF	Easy to perform, a cut off value > 38 has a predicts pre-eclampsia.	Only validated after 20 weeks' gestation (therefore too late to implement early aspirin use).
CTG	*Antenatal* The use of Dawes Redman criteria allows for non-subjective analysis with strong evidence of STV < 4 indicating fetal hypoxia and acidaemia. *Intrapartum* Allows for continuous and real time monitoring of fetal heart rate and uterine contractions. Reduces the risk of neonatal seizures by half compared to intermittent auscultation. Allows early recognition of rapid fetal wellbeing deterioration in acute events such as cord prolapse and placental abruption, identifying babies requiring urgent delivery.	Both resource and training dependent. Obstetric units using CTG both antenatally and intrapartum need to have the ability to provide regular training for staff on context specific interpretation and escalation of CTG. *Intrapartum* A high degree of subjectivity and susceptibility to operator misinterpretation. Does not reduce the risk of perinatal death or cerebral palsy, but increases the rate of cesarean section and operative vaginal delivery.
Growth charts	Few resources are required, scalable to all resource settings.	Population charts may not be applicable in highly heterogeneous populations, and customised charts do not reduce the incidence of SGA and may disproportionately. disadvantage women from ethnic minority background.
Fetal Doppler	Use of UA Doppler in the assessment of high-risk patients reduce risk of perinatal death., use of DV Doppler in early growth restriction is a good predictor of fetal compromise and reduces the risk of subsequent neonatal neurological deficits.	Highly operator and resource-dependent, inter-operator variability is a concern.
Fetal movements	Reduced and lack of movements correlate with poor outcomes (such as stillbirth and hypoxia). Progress being made towards optimising wearable fetal movement monitors.	Highly subjective, can cause maternal anxiety and repeated attendances to maternity services, relies on patient understanding of fetal movements and ability to access services, currently no clear package of care with demonstrated improvement in outcomes for RFM. Current commercial wearable fetal movement monitors are susceptible to noise and maternal movement artefacts.

The performance of an artificial intelligence (AI) ultrasound-based decision-analysis tool (OxNNET) trained with the largest 'ground data set' of over 2000 3D-US placental volumes has shown promising results in the prediction of SGA and high similarity to the gold standard 'manual segmentation' measurements, highlighting that the accuracy of the model can be greatly improved with a larger ground data set[61].

There has been rapid advancement in the use of Deep Learning in ultrasound, using many different algorithms, however, each algorithm has been developed using an individual ground data set. In order to create a universally applicable Deep Learning model, a large heterogenous ground data set will need to be developed and validated for use on the most commonly used commercial ultrasound machines before these methods can be fully automated. Despite these limitations, it is likely that in the near future, Deep Learning models in 1st trimester ultrasound represent a highly promising screening tool for placental insufficiency[62].

Magnetic resonance imaging (MRI)

MRI overcomes several limitations of ultrasound and is currently used to complement ultrasound for the assessment of fetal structures[63]. The most common indication is fetal brain abnormality as MRI has excellent soft tissue contrast, making it especially useful in assessing cortical development. Other fetal structural abnormalities where MRI can be useful include tumors of the face and neck, myelomeningocele, lung and diaphragmatic abnormalities and abnormalities of the bowel, kidneys and pelvis[63]. It is also valuable for assessment of the impact following such (e.g. spina bifida) surgery or after interventions for twin-to-twin transfusion (TTTS)[63].

The use of exogenous contrast agents in fetal MRI is rare. Widespread contrast agents are often based on Gadolinium, but it is known to cross into the brain[64]. Gadolinium contrast imaging has been used in placenta accreta prior to delivery to image the maternal blood supply[65]. Recent advances in iron-based contrast agents which have less potential toxicity have the potential to become the gold standard for measuring placental maternal perfusion[66]. In combination with oxygenation measurement, this could eventually lead to a comprehensive way of measuring placental haemodynamics and oxygen transfer.

Beyond structural imaging, different MRI contrasts are being used quantitively to gain information about tissue properties. The possibility of measuring placental and fetal oxygenation could be of clinical importance for assessing perfusion-modifying treatments in the case of FGR[67] or fetal anemia[68] or determining the effects of infection[69] on the function of the placenta and the necessity of subsequent delivery. The rapidity of T2* weighted imaging sequence has led to substantial progress in monitoring placental changes with maturation[70,71] and with pathology such as growth restriction[72]. Validation of the relationship between T2 weighted imaging and fetal blood oxygen saturation has recently been carried out in two independent techniques assessing fetal blood in both the umbilical cord[68,73] and the placenta[74,75] in sheep and human models[74,75]. There is also an increasing research interest in developing multiparametric computational models of placenta.

Both fetal ultrasound and MRI provide information on fetal well-being during single time points and for a limited time thereafter. As such, although undeniably valuable, especially from a scientific and research trial perspective, their non-continuous form, compounded by the limited availability of MRI in LMIC settings, renders them difficult to predict acute and unpredictable changes in fetal well-being globally.

Optical monitoring

Near-infrared Spectroscopy (NIRS) is an optical technology that uses NIR light (65–950 nm) to non-invasively monitor tissue oxygenation and hemodynamics in real time. NIRS has been extensively used for the assessment of neonatal brain injury and is currently part of the clinical practice in many neonatal neurocritical care units worldwide[76]. Peebles et al. first demonstrated the possible use of NIRS for fetal assessment and demonstrated a decline in cerebral blood volume with normal uterine contractions using NIRS probes attached to the fetal head[77]. With late decelerations, a clear drop in cerebral tissue oxygenation was noted[78]. In recent years, NIRS has also been explored for non-invasive measurement of placental oxygenation. The studies so far demonstrated the feasibility of monitoring and imaging placental oxygenation at the bedside continuously over several hours both during pregnancy and labor[79–82]. The predictive value of placental oxygenation for neonatal acidosis has been found to be superior to intrapartum CTG and fetal acidosis was associated with more episodes of deoxygenation[81]. Placental oxygenation was significantly lower in the presence of placental lesions and higher in pregnant women with fetal growth retardation (FGR) during pregnancy compared to pregnant women without complications[79]. Higher placental oxygenation was also noted before delivery in women with small for gestational age (SGA) babies and severe pre-eclampsia compared to women with normal fetal growth[82]. These studies highlight the relationship between placental oxygenation during pregnancy and labor with fetal outcomes. In addition to oxygenation, NIRS using a broadband light source can also monitor the oxidative state of cytochrome-c-oxidase (oxCCO) which is an enzyme in the mitochondrial respiratory chain. Therefore, broadband NIRS (bNIRS) can monitor both tissue oxygenation and energy metabolism[83]. Optical measures of oxCCO correlated with newborn brain metabolic markers quantified by MR spectroscopy during and after hypoxic injury and have been shown to be an important early biomarker for the assessment of injury severity and prognostication of outcome following hypoxic-ischemic encephalopathy[84,85]. Technological advances in this area led to the recent development of a multi-channel multi-wavelength enhanced time domain NIRS (TD NIRS) system which can overcome the limitations of commercial NIRS systems (depth penetration) and establish a gold standard real-time measurement of placental oxygenation and metabolism[86]. The ability of NIRS for non-invasive continuous monitoring of important physiological parameters in real-time gives it a significant advantage. This technology can head toward a successful clinical translation if the markers of placental tissue oxygenation and metabolism correlate with outcomes.

Digital biomarkers

Digital biomarkers fall within the scope of traditional biomarkers but with the use of digital and portable technology allowing for new dimensions to be obtained[87]. They often provide easy access to longitudinal and continuous measurements, with this being of particular use to draw diagnostic inferences from conditions that are hard to predict, or which occur over longer periods of time[88,89]. One key area that has seen significant growth is the use of machine learning to create useful tools and insights from the vast array of data collected in modern medicine[90].

Several biomarkers are currently available for fetoplacental monitoring, but without the ability to quickly and reliably process and analyse these biomarkers, the ability to prevent a negative outcome is severely limited. One of machine learning's (ML) great strengths is its ability to automate the analysis of data so that it can use learned "features" within the data to determine the probabilities of specific outcomes, be those diagnostics, prognostic or related to data quality. Additionally, one of the key use cases for ML within a clinical setting is as a clinical aid. Examples of this include the use of machine learning for risk stratification or to screen large quantities of data, allowing for more time to be spent by specialists on more complex tasks.

Artificial intelligence (AI) has also been explored to improve the diagnostic accuracy of obstetric ultrasound, for example, in measuring estimated fetal weights and gestational age[91]. Barbounaki et al. recently identified 32 studies covering the use of ML classifiers within the field of obstetrics and midwifery[92]. Focussing on neonatal mortality prediction, Slattery et al., developed a neural network to perform risk classification for HIE with a specificity of 81% in the case of a convolutional neural network[93]. In fetal monitoring, Arnaout et al., utilised another convolutional deep learning approach that was able to identify hypoplastic left heart syndrome with a specificity of 100% and a sensitivity of 90% across a dataset of 685 echocardiograms[94]. Finally, Jhee et al., were able to use a stochastic gradient

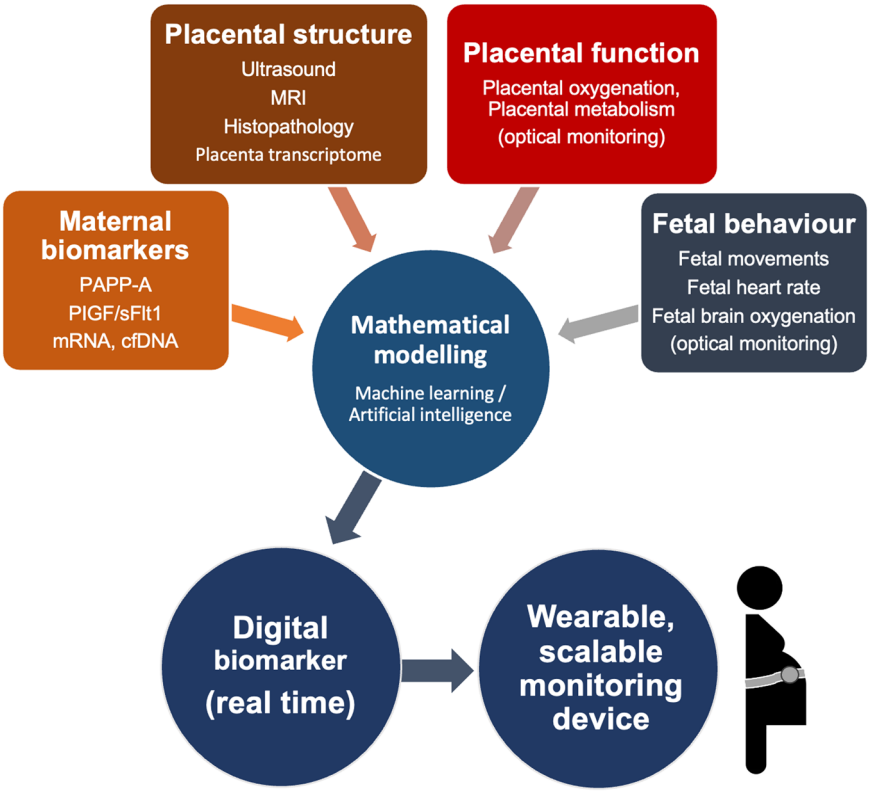

Fig. 1 | The ideal fetoplacental monitoring tool. Multi-modal inputs from both fetal and maternal parameters are required to build the future gold standard fetoplacental monitoring system.

boosting model to identify late-onset preeclampsia with an accuracy of 0.973 and a false-positive rate of 0.009[95].

Whilst there are clear strengths to using ML within antenatal care, both ML and digital biomarkers as a source of data require care when looking at their integration and adoption. Some of the challenges faced in the integration of digital biomarkers into clinical care include the quality of data, data storage, privacy and interpretation, and obtaining regulatory approval for tools that are the product of rapid development and innovation[87]. The considerations around data storage and privacy can all be handled through careful engineering of the data processing and storage pipelines and platforms, whilst analytics and regulatory approval in particular are more nuanced but still approachable challenges. One of these is a problem that is faced in any application of ML algorithms, and that is for a model "to operate accurately, large, high-quality training datasets are required, as small or poor-quality ones could lead to inferior outcomes"[92].

When considering the use of ML and AI as effective tools within a clinical setting there are several additional considerations that must be taken into account before it can be applied in a real-world environment. Firstly, is that the algorithm should be "explainable". This is of particular importance when using it to make a diagnostic or prognostic classification - determining why an outcome has been predicted is as important as what that outcome is. There is a significant amount of work already being undertaken within this field of Explainable AI (XAI), not just within digital healthcare. There are a few different ways to approach XAI and these often depend on the algorithm being used. For example, in the case of a pipeline where features are determined explicitly by clinicians and researchers, it is possible to use "feature importance" to determine which of these are most important and some algorithms, such as the Random Forest algorithm, can determine feature importance directly. In contrast, deep learning models, or neural networks, are typically used to determine their own patterns and features from data and are very much seen as black boxes. This flexibility is why they have seen such a varied set of use cases and can be used to process multiple data types, but it also makes them harder to interpret from a clinical standpoint.

The second key challenge facing the integration of ML into clinical care, is algorithmic bias. This is the inherent bias introduced into a model by the decisions and choices made by researchers and engineers at the training stage. The choice of dataset, performance metrics and success criteria will all contribute to the internal design of an algorithm. Learned parameter values will all depend on how the model is trained and what it is trained on, and these are what effectively determine the model outcomes. Algorithmic bias can be considered a specific subcategory of model overfitting i.e., poor generalisation. Looking specifically within healthcare, those from marginalised backgrounds are likely to be underrepresented within datasets used to train algorithms which would further compound inequities[96].

Whilst these problems are to a large degree systemic, there are several possible approaches to tackle these. Firstly, awareness of the systemic bias that can lead to algorithmic bias can help us to mitigate the latter. Choosing to create a diverse and varied pool of data from the start can help to reduce the risk of only selecting and using data that comes from overrepresented groups as opposed to underrepresented ones. Another key approach is to constantly and consistently retrain models with new data during the lifetime of its use, ideally through good MLOps practice[97]. This allows models to be kept up to date and for the pool of data used to train them to be kept as large and as representative of the real use-case population as possible. Another part of this is to constantly monitor and validate models against subsets of new data to avoid the potential for "model drift", where the model drifts from its original performance metrics due to the use against new data. This could be because the real-world data population is significantly different from the training data sample used, or it could be because the use of machine learning influences outcomes itself e.g., it improves diagnostic capabilities thus influencing prognosis.

It is beyond the scope of this article to include every single evolving direction of work to improve fetoplacental outcomes. It is likely that future progress in this area depends on combining different markers of fetal behavior, placental function, placental structure and maternal health to develop digital biomarkers using scalable wearable monitoring tools for continuous real-time detection of changes (Fig. 1).

Conclusion

The mainstay of fetoplacental monitoring in day-to-day obstetric practice is ultrasonography (USS) with electronic fetal heart rate monitoring (CTG), which has several limitations. Current techniques of antenatal monitoring provide only a 'snap-shot' of surrogate markers of fetoplacental function at certain fixed time points. Unfortunately, we still do not have the necessary tools to provide a continuous method of effective monitoring and capturing physiological information to identify acute deteriorations in function outside of the hospital setting. The ability to monitor targeted 'at risk' subgroups of patients with an appropriately sensitive tool may provide a window of opportunity for intervention, prior to significant fetal compromise.

It is clear that there is an urgent need to support or replace existing monitoring methods with more accurate non-invasive tools that can lead to a better identification of pathophysiological changes and predicting outcomes. The ideal fetoplacental monitoring tool would need to be accurate, non-invasive, affordable and easily scalable for use, particularly in out-of-hospital and low-resource settings. Future monitoring techniques should also be able to utilise digital technology and the rapidly developing field of machine learning and the use of artificial intelligence, to reduce human error but also to allow remote monitoring at home to improve accessibility and continuous monitoring for all (Fig. 1). Miniaturised wearable optical systems, with or without CTG in combination with advanced analytics based on artificial intelligence algorithms have the opportunity to revolutionise fetoplacental monitoring in both in-hospital and at-home settings. The development of digital biomarkers for fetoplacental monitoring together with technological advances in wearable technologies brings promise for the development of an exciting future solution to save babies and their families from any preventable harm.

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Author contributions

N.R.Z. and S.M. conceptualised the review. N.R.Z. and S.M. prepared the first draft. All authors reviewed, contributed to and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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