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TOPICAL REVIEW

Fetal monitoring technologies for the detection of intrapartum hypoxia - challenges and opportunities

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Abstract

Intrapartum fetal hypoxia is related to long-term morbidity and mortality of the fetus and the mother. Fetal surveillance is extremely important to minimize the adverse outcomes arising from fetal hypoxia during labour. Several methods have been used in current clinical practice to monitor fetal well-being. For instance, biophysical technologies including cardiotocography, ST-analysis adjunct to cardiotocography, and Doppler ultrasound are used for intrapartum fetal monitoring. However, these technologies result in a high false-positive rate and increased obstetric interventions during labour. Alternatively, biochemical-based technologies including fetal scalp blood sampling and fetal pulse oximetry are used to identify metabolic acidosis and oxygen deprivation resulting from fetal hypoxia. These technologies neither improve clinical outcomes nor reduce unnecessary interventions during labour. Also, there is a need to link the physiological changes during fetal hypoxia to fetal monitoring technologies. The objective of this article is to assess the clinical background of fetal hypoxia and to review existing monitoring technologies for the detection and monitoring of fetal hypoxia. A comprehensive review has been made to predict fetal hypoxia using computational and machine-learning algorithms. The detection of more specific biomarkers or new sensing technologies is also reviewed which may help in the enhancement of the reliability of continuous fetal monitoring and may result in the accurate detection of intrapartum fetal hypoxia.

1. Introduction

Hypoxia is a lack of adequate oxygen supply to a region of the body at a tissue level [1]. Hypoxic tissues compromise normal cell function, which may lead to serious cell pathology, stillbirth, or neonatal death. Regardless of the significant benefits of hypoxia-assisted degranulation, such as enhanced pathogen disposal and increased neutrophil access to the sites of infection, toxic granule products are more likely to induce systemic issues and local tissue injury [2]. Hypoxia during labour, known as intrapartum hypoxia, accounts for 2.2 million intrapartum and early neonatal deaths annually [3]. On average, 130 million babies are born globally in a year, with 4 million infants dying during labour and 26% of these as intrapartum stillbirths [4]. Additionally, every year intrapartum hypoxia results in up to one million children born with life-long disabilities. These disabilities may include a range of neurological conditions [4]. Cummins *et al* suggested a direct and important link between the incidence of fetal hypoxia, consequent outcomes, and the levels of obstetric care and continuous clinical monitoring practice [5]. The incidence of intrapartum-related deaths is higher in low- and middle-income countries where obstetric care and monitoring are poor compared to developed countries [3]. As an example, the overall rate of stillbirths and early neonatal death in South Africa is reported as significantly higher (4.8 per 1000 births) compared to the United Kingdom (0.9 per 1000 births) due to a lack of proper obstetric care and inadequate

fetal surveillance during labour [6]. Minimization of fetal and neonatal mortality and morbidity due to hypoxia requires mandatory continuous intrapartum fetal monitoring and assurance of early detection [7]. Methods of such monitoring have evolved with so-called electronic fetal monitoring now an essential part of the monitoring strategy facilitating continuous monitoring of the fetus. This continuous electronic fetal monitoring was introduced in the late 1960s but before this point devices such as the Pinard stethoscope and hand-held Doppler, units were used and specifically designed for auscultation of fetal heart sounds, and in particular monitoring the fetal heart rate (FHR). This type of monitoring is called Intermittent Auscultation (IA). IA refers to periodic monitoring of the fetal heart parameters at typically five to thirty-minute intervals during the first stage of labour, and every five minutes or after each uterine contraction in the second stage of labour. Therefore, IA provides intermittent records of fetal heart sounds and FHR usually without a display provided. By using IA, fetal hypoxia can be deduced from abnormal FHR [8–10]. However, there are no established IA protocols and challenges exist in ensuring the accuracy of IA as a monitoring modality [11].

Electronic fetal monitoring (EFM) also known as cardiotocography (CTG) was introduced as a continuous intrapartum fetal surveillance method for the early detection of fetal hypoxia facilitating timely obstetric decisions and interventions if required during labour. Continuous surveillance by EFM is uninterrupted with constant measurement of FHR and uterine contractions (UC) by an electronic fetal monitoring device, with the recording stored as a CTG tracing (called a cardiotocogram) [9]. The cardiotocogram is then used to manage labour and make clinical decisions based on the interpretation of the FHR using specific criteria of CTG analysis [12]. CTG is recommended in high-risk pregnancies and is usually encountered more in higher-income countries as the modality is both time-intensive and expensive. Therefore, in low-resource settings and for low-risk pregnancies IA is more generally utilized [13]. Ideally, however, IA is not recommended as a sole monitoring technique especially in high-risk pregnancies [14].

Despite the apparent advantages of EFM and the use of the technology for nearly five decades, it has been associated with a continuous and substantial increase in the number of obstetric interventions without a corresponding reduction in metrics such as perinatal mortality rate and incidence of permanent neurological sequelae [15]. Some recent studies have also reported controversy and uncertainties attributed to the use of EFM in clinical routine practice [14, 16, 17]. As an example, the technology is associated with a low positive predictive value (30%) and a high false-positive rate (around 60%) [15]. A recent Cochrane systematic review has indeed challenged the effectiveness of EFM during labour [18]. The authors compared CTG with IA analysing the outcomes of 13 trials including more than 37,000 women. The review concluded that there was no difference in the rate of perinatal deaths and incidence of neurological hypoxic injuries among women monitored with CTG compared to IA, while CTG was associated with a substantial increase in the frequency of obstetric interventions caesarean sections, and assisted vaginal birth using instruments [18]. Additionally, respected bodies such as the International Federation of Gynaecology and Obstetrics (FIGO), and the National Institute for Health and Care Excellence (NICE) have reported findings similar to Alfirevic *et al* agreeing that there is unclear and insufficient evidence that humans or indeed the computerized interpretation of cardiotocographs reduce the rates of adverse outcomes such as intrapartum stillbirth or cerebral palsy [18]. In another study at the INFANT research centre, the authors highlighted the uncertainties in the computerized decision-making process and showed that EFM did not improve clinical outcomes for the fetus or mother [17]. The main motivation behind the introduction of EFM was expected improvements in intrapartum fetal monitoring, better management of intrapartum fetal hypoxia, and an improvement in fetal outcomes as seen by reductions in mortality and morbidity. However, as described the use of EFM in clinical practice is instead still controversial. Consequently, intrapartum fetal surveillance often requires continuous, non-invasive, and real-time alternative or adjunct technologies for the better detection and clinical management of fetal hypoxia [15, 19]. This recent evidence suggests that there is a need for improvements in the area of fetal monitoring.

Further investigation and research into the links between intrapartum hypoxia, fetal physiological changes resulting from hypoxia, related physiological parameters that could be used for monitoring, and ultimately fetal outcome is required which can then be translated into effective technologies. The previous studies have demonstrated the clinical background of fetal hypoxia [5, 20, 21], fetal response to hypoxia [22], fetal monitoring technologies [23], findings for fetal monitoring technologies [24–26] and signal processing techniques [27–29] extensively. However, most of these reviews focus only on individual subjects of fetal hypoxia. This review article presents both medical and technical perspectives of fetal hypoxia to identify the advancements in the field. In this article, a comprehensive review is conducted to review the challenges and opportunities in fetal monitoring technologies for the detection of intrapartum hypoxia. In this paper, the clinical background of fetal hypoxia is reviewed, alongside the physiological mechanisms seen in hypoxia, and current electronic fetal monitoring technologies. The main focus of this article is a review of these existing fetal monitoring technologies examining the advantages and limitations of each one in clinical practice. This work presents a comprehensive

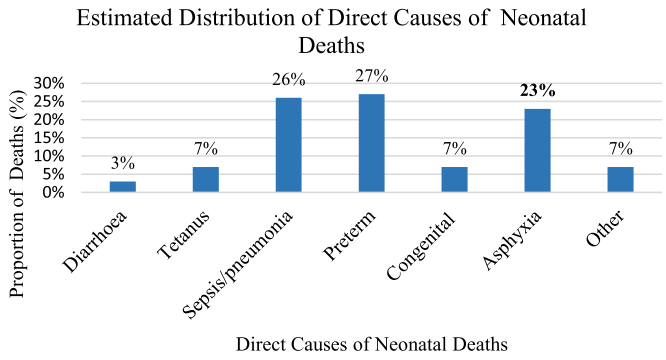

Figure 1. Estimated distribution of direct causes responsible for the annual 4 million neonatal deaths. Reprinted from [4], Copyright (2005), with permission from Elsevier.

resource that also examines basic components of ECG analysis including ECG features extraction, and computational and machine learning algorithms to classify the ECG signal. The characteristics of an ideal fetal monitor, and how novel and emerging sensing technologies can help to enhance continuous fetal monitoring and intrapartum hypoxia assessment are also examined.

2. Clinical background

This section examines the epidemiology of fetal hypoxia and the effects of hypoxia on both the child and the mother. The significant morbidity and mortality associated with the condition as discussed in this section, further emphasizes the need for effective monitoring technologies for the condition.

2.1. Epidemiology of fetal hypoxia

In adults, the functioning and viability of all cells are dependent on a constant supply of oxygen from arterial blood [30]. For the developing fetus, fetal oxygenation is completely regulated by the maternal respiratory and circulatory systems as well as by the efficiency of the placental and fetal blood circulations. During labour, disruption of these systems may induce oxygen deficiency in fetal arterial blood called hypoxemia, which may increase the risk of fetal loss [1]. The primary condition/issue associated with fetal hypoxia is metabolic acidosis. Metabolic acidosis refers to an imbalance in the acid–base balance of the body often as a result of increased production of lactic acid [31]. During hypoxia, insufficient oxygen may elevate carbon dioxide contents, carbon dioxide, and carbonic acid constituting hypercapnia. Intrapartum hypoxia with hypercapnia and metabolic acidosis constitutes asphyxia [32]. World Health Organization (WHO) has defined birth asphyxia as 'failure to initiate and sustain breathing at birth' [33]. Globally about 23% of the annual neonatal deaths are directly accounted for by birth asphyxia (see figure 1). Hence, intrapartum hypoxia may be considered a global burden mainly due to this high mortality and morbidity rate, particularly in low-income countries. According to the Global Burden of Disease 2010 study, intrapartum-related impairments were estimated at 50.2 million disability-adjusted life years (DALYs) which is a double figure than the DALYs compromised by diabetes [34].

During intrapartum fetal hypoxia, poor obstetric care and monitoring may result in unnecessary interventions that adversely affect the fetus as well as the mother. According to a report by Hill *et al* about 500,000 maternal deaths were reported in 2005 with about half of these mothers dying during labour, defined as intrapartum-related maternal deaths [35]. Most of the deaths arose primarily in low-income and middle-income countries due to the unavailability of professional intrapartum care [4, 36]. Waters *et al* performed a population-based study for California state hospitals in 2005 where 576,846 mothers were admitted for obstetric intervention, only 7% of these admissions were categorized as antepartum or postpartum while 93% of admissions were identified as intrapartum [37] which indicates that the vast majority of maternal complications arise during the crucial intrapartum period.

These epidemiological data suggest there is a need for extensive research to better understand the pathophysiology of intrapartum hypoxia and to define the link between hypoxia and intrapartum obstetric care. Better monitoring technologies may then give the accurate surveillance needed to minimize intrapartum-related injuries and their consequences.

3. Physiological and pathophysiological mechanism

In this section, the origin and causes of fetal hypoxia are discussed as well as a categorization based on the underlying cause. Next, a review of an established second method of categorization of intrapartum fetal hypoxia into four distinct types based on the speed of onset is presented. The pathophysiology of the condition is then examined by analysis of the stages of progressively worsening hypoxia and the fetal

responses to hypoxia. Finally, potential biomarkers that are directly related to the pathology and the homeostatic responses by the fetus and are used by some existing monitoring technologies are reviewed.

3.1. Aetiology of fetal hypoxia

The fetus maintains oxygenation levels as oxygen moves through maternal respiration and circulation, to the umbilical cord, through the placental gas exchange system, to placental perfusion, and finally into fetal circulation [1]. Oxygen diffuses into the fetal circulatory system and is facilitated by factors including an elevated partial pressure of maternal oxygen, the lower partial pressure of fetal oxygen, and the increased affinity of fetal blood for oxygen [38]. Conversely, the placenta removes carbon dioxide produced during metabolism from the fetal circulation into the maternal circulation. Disruption in these systems at any stage of fetal life causes fetal hypoxia characterized by a subsequent decrease of oxygen in arterial blood and the tissues served by this blood supply [1].

Failure of this placental perfusion system may cause an accumulation of carbon dioxide (CO_2) in the fetal tissues. The accumulation of CO_2 is known as respiratory acidosis and is characterized by the high partial pressure of carbon dioxide (pCO_2) in the fetus. Failure of placental perfusion may also lead to oxygen deprivation. This deprivation can initiate anaerobic metabolism, which results in metabolic acidosis. In metabolic acidosis, the accumulated CO_2 combines with plasma to form carbonic acid which splits into bicarbonate ($HCO3^-$) and hydrogen ion (H^+) and results in a lowering of the fetal pH [39].

Various physiological and pathological conditions may induce fetal hypoxia during pregnancy and labour. Inadequate oxygen supply to the fetus, which leads to fetal hypoxia, is relatively common and may not always result in adverse outcomes. As a result of inadequate oxygen supply, the fetus implements compensatory mechanisms in an attempt to restore normal oxygen levels. For example, uterine contractions can temporarily decrease blood flow, but it may not result in adverse outcomes in the healthy uncompromised fetus due to compensation mechanisms. During a contraction, fetal preload increases, which ensures a constant blood flow through the umbilical artery. Additionally, the brain-sparing effect also compensates for the decreased umbilical artery blood flow and oxygen saturation [40].

While the majority of fetuses can naturally adapt to these insults of labour, compromised fetuses or excessive uterine activity can increase the risk of adverse outcomes [Ref]. Moreover, these mechanisms may fail if the hypoxic insult is sufficiently severe or sustained long enough, resulting in adverse consequences for the fetus. Another example of a compensatory mechanism is anaerobic metabolism which is a biochemical system designed to maintain energy production in the absence of oxygen [41]. However, a by-product of anaerobic metabolism is lactic acid, which will cause an increase in blood acid levels (i.e., an increase in blood H^+ concentration, measured as a reduction in pH). This decrease in pH value may result in neurological sequelae such as cerebral palsy [42]. The incidence of neurological disorders including cerebral palsy caused by perinatal hypoxia is 1 per 300 term live births [43]. In developed regions, 17.2% of infants that had hypoxia have permanent neurological disorders, 16.3% have epilepsy and 5.9% of neonates die. Furthermore, circulatory issues during pregnancy, problems with placental arteries, placental abruption, or inflammatory processes can lead to reduced oxygen exchange, resulting in severe lactic acidosis [44].

Intrapartum fetal hypoxia, characterised by insufficient oxygen supply during crucial stages of labour and delivery, can have serious implications and potentially result in a more severe condition known as hypoxic-ischemic encephalopathy (HIE) [45, 46]. HIE is a condition where there is insufficient oxygen and blood flow to the brain, leading to neurological damage and long-term disabilities, including cognitive impairments and cerebral palsy. HIE typically manifests as hypoxic-ischemic encephalopathy, characterized by seizures, abnormal EEG activity, hypotonia, feeding difficulties, and altered consciousness [44–47]. The incidence of hypoxic-ischemic encephalopathy (HIE) is 2.5 per 1000 term live births and a higher incidence is observed in less developed countries ranging from 5.5 to 26.5 per 1000 live births [48]. As well as neurological sequelae, intrapartum hypoxia may also cause pathology in other systems. Organs and systems such as the gastrointestinal tract, kidneys, spleen, and liver may be affected as a result of hypoxia-caused blood redistribution away from these tissues, or as a result in a decline in cardiac output [49]. For example, acute tubular necrosis (damage of kidney cells) leading to dysfunction of the renal system may come as a consequence of fetal hypoxia [22]. Fetal hypoxia may also introduce common pulmonary complications including structural and functional lung disorders [22]. Additionally, fetal hypoxia secondary to maternal anaemia may also be responsible for the cutaneous manifestations e.g. blueberry muffin-like lesions [50].

In particular, the risk of adverse fetal outcomes during the intrapartum period is highly associated with complications during labour [36]. These physiological conditions are associated with embryonic development, implantation of the placenta into the uterine wall, and fetal growth, whereas pathological conditions are related to maternal and fetal diseases [51]. The aetiology of fetal hypoxia can be divided into three different categories based on whether the fundamental cause of impaired oxygen supply is before, at, or after the placental implantation. Kingdom *et al* proposed a three-category model on the origin of fetal

hypoxia [52]. These categories are respectively known as:

- Pre-placental Hypoxia
- Utero-placental Hypoxia
- Post-placental Hypoxia

Post-placental hypoxia is directly related to intrapartum fetal hypoxia while pre-placental and uteroplacental categories increase the susceptibility of intrapartum hypoxia during labour [20].

3.2. Types of intrapartum hypoxia

The categorization of fetal hypoxia as pre-placental, uteroplacental, or post-placenta relates to the aetiology. Regardless of the underlying cause, intrapartum fetal hypoxia can also be further categorized based on the speed of onset and duration of hypoxia [49], with a division into:

- Acute Hypoxia
- Subacute Hypoxia
- Gradually Developing Hypoxia
- Long-Standing Hypoxia (Chronic Hypoxia)

The variations in signs and symptoms of intrapartum hypoxia as assessed using fetal monitoring can be used to decide on the type of hypoxia. This latter categorization based on the speed of onset and duration is important from a monitoring perspective as it helps to decide on the timing and type of obstetric intervention. However, in addition to a categorization of hypoxia type other factors such as the maturity of the fetus, and the degree of fetal response to the hypoxic insult are also considered when making decisions on obstetric intervention [53]. Acute hypoxia can be defined as the short-term deprivation of oxygen lasting a few minutes (6–9 min) during childbirth [54]. Acute hypoxic episodes may occur due to umbilical cord prolapse, uterine scar dehiscence, placental abruption, oxytocin-induced uterine hyperstimulation, and epidural analgesia [59]. Other factors such as the compression of the umbilical cord due to uterine contractions, stress applied to the fetal head during the obstetric intervention, epidural analgesia, and vaginal examination can also lead to acute intrapartum hypoxia [23, 39, 57]. In some cases, acute hypoxia may be too short-acting to be detrimental such as in some cases of epidural analgesia and vaginal examination, and further can be managed with careful monitoring, adjustment of maternal position, discontinuation of oxytocin infusion during active labour, and regulation of maternal hydration and oxygenation [39, 53, 58, 59].

CTG patterns, especially accelerations and decelerations, have been traditionally considered crucial indicators that can help identify signs of intrapartum hypoxia. Accelerations in CTG patterns are characterized by transient increases in FHR and are widely recognized as indicative of fetal well-being during labour [60]. On the other hand, decelerations characterised by temporary decreases in CTG below the baseline can be indicative of hypoxia and compromised fetal well-being [61]. Decelerations in FHR are classified into three principal patterns based on their timings relative to uterine contractions: early decelerations, variable decelerations, and late decelerations [62, 63]. Late decelerations, which typically follow the peak of contractions, are of particular importance in identifying signs of hypoxia during labour [61]. However, recent evidence suggests that decelerations in fetal heart rate may not be sensitive enough to accurately indicate intrapartum deterioration [64].The initial signs of acute hypoxia feature late decelerations along with an increase in baseline variability due to the secretion of catecholamines [58, 59]. A prolonged deceleration or bradycardia lasting for six minutes or more with FHR less than 80 beats per minute (bpm) is associated with acute hypoxia [53]. For example, figure 2 depicts acute hypoxia due to uterine rupture where the loss of baseline variability within 3 min of deceleration and sudden fall in FHR is below 80 bpm. During acute hypoxia, a sudden and rapid metabolic acidosis occurs with a decrease of pH at a rate greater than 0.01 per minute [65]. Acute hypoxia requires proper monitoring to prevent the risk of progression into subacute hypoxia [49].

Subacute hypoxia develops over 30 to 60 min. During subacute hypoxia, a rapid drop in pH can be observed along with variations in the normal patterns of FHR and rhythm. A deceleration pattern lasting 90 seconds or more and a normal baseline lasting less than 30 seconds are characteristic FHR patterns of subacute hypoxia [39, 66] (see figure 3). This prolonged deceleration results from a compensatory response by the fetus designed to protect the heart and brain. The deceleration also leads to a decline in fetal gas-exchange ability which takes almost three times the usual time. [65]. This insufficient time to get the required amount of oxygen for the fetus initially induces respiratory acidosis (an accumulation of carbon dioxide in the fetus due to poor placental perfusion), which can eventually lead to metabolic acidosis. A reduction in pH implies an accumulation of acid in the fetus. In subacute hypoxia, fetal pH declines at the rate of 0.01 over 2–3 min, and this rate of decrease in pH can accelerate when high-risk factors are also present such as meconium stained-amniotic fluid, fetal growth retardation, and fetal or maternal infections [32].

Failure of placental perfusion from maternal to fetal circulation also leads to oxygen deprivation. This deprivation can initiate anaerobic metabolism, which results in metabolic acidosis. Metabolic acidosis generates fetal stress which can lead to gradually developing hypoxia or fetal distress. This period is termed the 'stress-to-distress period' and it may last about four hours depending on

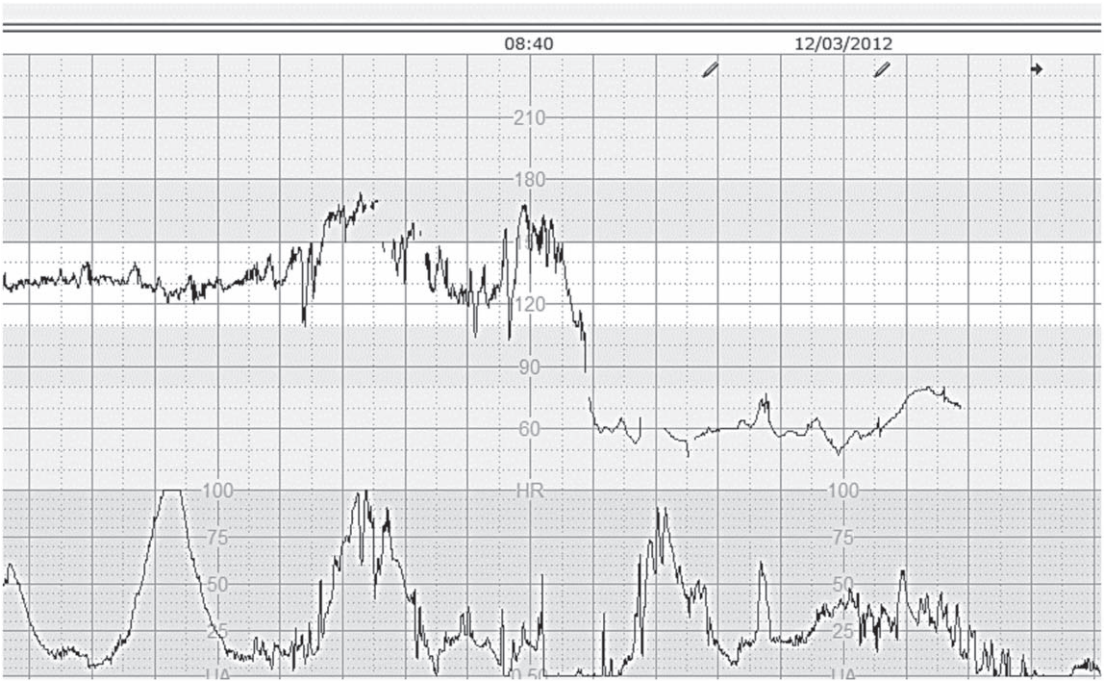

Figure 2. Acute Hypoxia with a sudden drop in FHR below 80 bpm also with a deceleration pattern lasting for 90 seconds. Reprinted from [66], Copyright (2016), with permission from Elsevier.

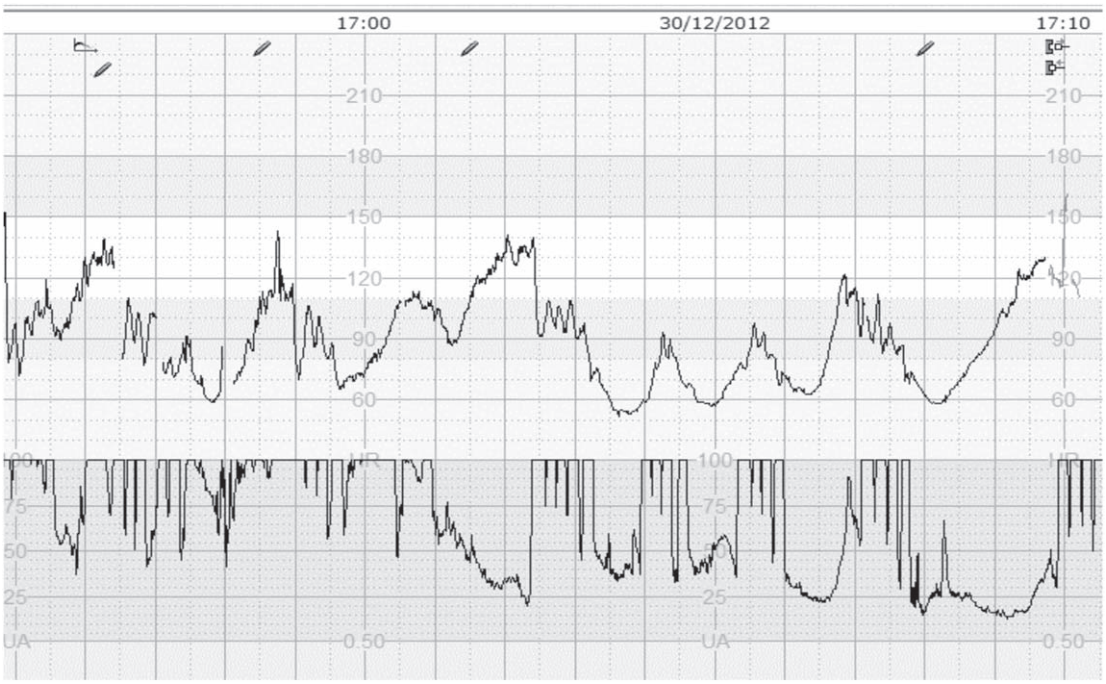

Figure 3. Subacute Hypoxia with more time spent during decelerations as compared to normal baseline. Reprinted from [66], Copyright (2016), with permission from Elsevier.

the fetal physiological reserve and compensatory mechanism. The overall duration for gradually developing hypoxia is not predictable and it could last for several hours depending upon the fetal condition with a gradual increase in fetal heart rate [39]. During the initial stages of a gradually developing hypoxia, accelerations in the FHR start to disappear, and decelerations begin to emerge [39]. Then, the duration and intensity of decelerations are increased in a consistent manner accompanied by a rise in the baseline and rise in FHR called the distress period. This period may last up to three hours. The rise in the baseline is due to the release of catecholamine hormones, a compensatory mechanism to increase cardiac output. The rise in baseline FHR and

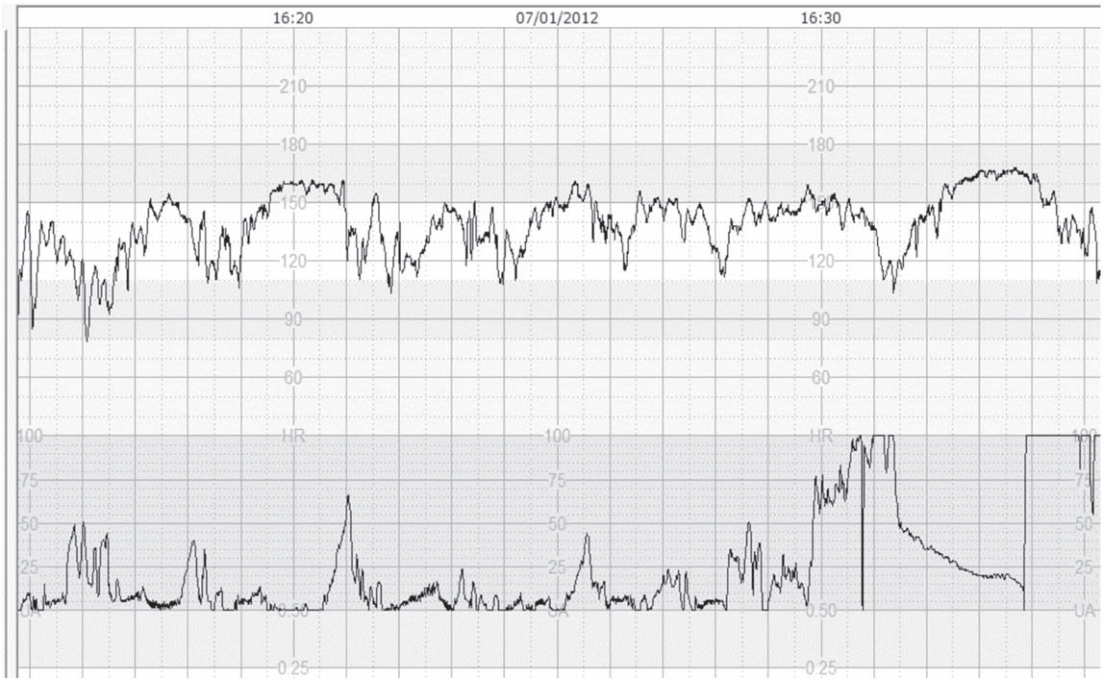

Figure 4. Gradually Evolving Hypoxia with the absence of accelerations, the presence of repetitive decelerations, and a rise in FHR baseline. Reprinted from [66], Copyright (2016), with permission from Elsevier.

the absence of accelerations depict the ongoing deprivation of oxygen (see figure 4). Depending upon the fetal glycogen reserve, severity, and duration of hypoxia, the persistent hypoxic condition may lead to the development of metabolic acidosis. The FHR patterns can be used to identify different phases of a gradually developing hypoxia such as the duration and onset of stress, stress-to-distress, and distress period [32]. These patterns can be assessed by IA or by EFM methods, and other diagnostics such as fetal pH and blood gas levels can also be used. Confirmation of a gradually developing hypoxia often necessitates urgent decisions on the time and type of operative delivery [67]. A failure to recognize important pathological patterns or failure to decide on proper intervention can lead to significant fetal morbidity and even mortality. The final 'distress-to-death' period (approximately 40 min) is characterized by terminal bradycardia and fetal mortality [66].

A gradual deprival in the fetal oxygen level lasting several weeks or even months during pregnancy can be classified as longstanding or chronic hypoxia. The primary reasons behind chronic hypoxia are placental inefficiency, as well as malnutrition in the mother. Maternal malnutrition may lead to obesity, gestational diabetes, gestational anaemia, or intra-amniotic infection. In gestational diabetes, both fetal hyperglycaemia (elevated blood glucose) and fetal hyperinsulinemia (elevated insulin levels) can independently increase oxygen consumption levels, thereby decreasing the fetal arterial oxygen levels [68].

Chronic hypoxia developed during pregnancy will compound the consequences of intrapartum hypoxia. During chronic hypoxia, the fetus adapts to the chronic hypoxic environment by redistributing the blood to the vital organs. This results in abnormal fetal birth weight, due to stunting in the growth of some organs [66]. Also, hemopoietic mechanisms are upregulated to compensate for the decreased availability of oxygen. An increase in immature nucleated red blood cells (RBCs) is seen, as well as an increased level of the hormone erythropoietin (EPO) hormone. EPO is secreted by the kidneys and is used to produce RBCs, with levels measurable in the amniotic fluid. The presence of immature RBCs and elevated EPO levels are considered indicators of chronic hypoxia [69, 70].

In chronic hypoxia, the baseline variability of the fetal heart rate pattern may be reduced, and a flat baseline may be observed. A flat baseline or lack of baseline variability related to metabolic acidosis may be more dangerous than a baseline with decelerations [58]. The FHR pattern may exhibit shallow, late decelerations along with missing accelerations and an absence of cycling behaviour, indicating a hypoxic fetus. Figure 5 depicts chronic hypoxia with reduced variability and shallow decelerations. Also, in the chronic hypoxic fetus, the occurrence of an impulsive event such as uterine contractions can cause a deterioration in the condition of the fetus since the fetal physiological reserves are already reduced [65]. Chronic hypoxia can increase the risk of preterm birth, fetal growth complications (for example intrauterine growth retardation, fetal macrosomia, or fetal overgrowth), a high stillbirth rate, especially in the last weeks of pregnancy, and adverse neurological outcomes after birth [53, 68].

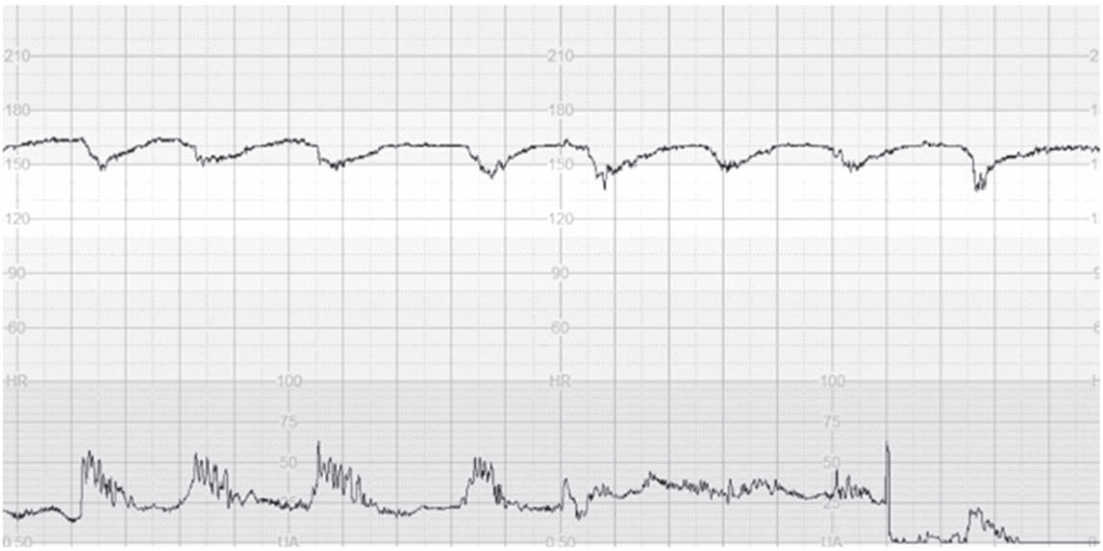

Figure 5. Chronic Hypoxia with increased baseline, shallow deceleration, and reduced baseline variability. Reproduced from [71]. CC BY 4.0.

3.3. Stages of intrapartum fetal hypoxia

The depletion of oxygen during intrapartum fetal hypoxia can be divided into three stages depending on severity [72].

- Mild Hypoxia: transient hypoxemia without metabolic acidosis
- Moderately Severe Hypoxia: tissue hypoxia with a risk of metabolic acidosis
- Asphyxia: tissue hypoxia with metabolic acidosis

During the first stage of mild hypoxia, the oxygen level starts to deteriorate and falls below normoxic oxygen levels. Such normoxic levels are defined as oxygen demand for a healthy fetus during pregnancy. For instance, at the early stage of pregnancy hypoxic environment is crucial while at later gestational stages, oxygen supply and nutrient demand are increased for the healthy growth of the fetus [73]. A 'reassuring FHR pattern' is observed for a healthy fetus with an adequate amount of oxygen to the fetal central organs (myocardium and brain). A change to a 'compensatory FHR pattern' generally indicates mild hypoxia [49]. Mild hypoxia also causes an initial compensatory adaptation featuring bradypnea (abnormally slow breathing) in neonates [74].

Moderately severe hypoxia is the second stage of fetal hypoxia. This second stage sees a drop in fetal oxygenation level to at least 30% below normal levels, along with metabolic acidosis often being present [59]. A 'non-reassuring FHR pattern' is also present. The fetal response to prolonged tissue hypoxia in this stage is known as stable compensation. This compensation may cause apnoea, cessation of oxygen supply lasting for 15 seconds, or more in neonates [49].

The third stage of fetal hypoxia, asphyxia, is defined as a drop in oxygen levels to below 50% of normal levels, as well as metabolic acidosis being present [59]. An 'ominous FHR pattern' may be present, as well as the possibility of fetal gasping [49]. This stage of hypoxia is also linked with high-risk pregnancies characterized by conditions such as preeclampsia, hypertension, and intrauterine growth restrictions. The probability of the fetus going into a state of decompensation followed by significant morbidity and even mortality is higher in the case of asphyxia [75].

A depletion in the levels of oxygen stimulates compensatory mechanisms and generates variations in the FHR patterns. The nature of the compensatory mechanisms and FHR patterns will depend on the stage of hypoxia as described. As part of intrapartum care, each stage must be carefully diagnosed and monitored to ensure appropriate clinical management and intervention if needed [76].

3.4. Fetal defensive response to hypoxia

The fetal defensive response to hypoxia involves a series of compensatory mechanisms that are activated to try to maintain oxygen homeostasis. This oxygen homeostasis is a self-regulating system designed to maintain oxygen levels in the body [73]. Depending upon the nature of hypoxia, a fetus can use several defensive mechanisms including the cellular, cardiovascular, autonomic nervous system, and haematological (relating to blood) responses [77]. These compensatory responses are now briefly reviewed:

3.4.1. Cellular response

The initial reaction of the fetus to hypoxia is to trigger a response at the cellular level to increase oxygen delivery [73]. The principal regulator of oxygen homeostasis is a transcriptional DNA-binding gene called

Hypoxic-Inducible Factor-1 (HIF-1). This gene controls the expression of more than 70 genes associated with cell adaptation to hypoxia [51, 78]. This cellular response against mild hypoxia is complemented by alterations in genetic expressions of cells that are responsible for the fetal metabolic process, inflammatory responses, and adaptive immune system [79]. Depending upon the severity of hypoxia, the cellular response may be compromised and alterations in gene expression may also come as a consequence of fetal heart abnormalities including abnormal structural and functional development of the heart [80].

3.4.2. Cardiac response

The cardiac response features a redistribution of the blood flow to vital organs such as the placenta, the myocardium (heart muscles), adrenal glands, and the brain. This response is triggered by peripheral chemoreflex particularly in acute and transient intrapartum hypoxia to maintain cardiac output. Of particular note, is the 'brain sparing effect' where generalized peripheral vasoconstrictor and cerebral vasodilation preferentially supply the brain with blood and minimize the hypoxic damage [81].

This redistribution of blood to vital organs is mostly seen in the initial stages of intrapartum hypoxia. Animal studies have shown that in the absence of metabolic acidosis, the fetus can maintain its protective cardiovascular adaptations including redistribution of blood flow and metabolic adjustments. However, this compensatory mechanism may begin to deteriorate with the development of metabolic acidosis, particularly with pH $<$ 7.0, with the resulting loss of function in multiple organs. For instance, the central nervous system and the brain, with the failure of the compensatory system, may lead to potential neurological disorders as well as cardiac cell injury with the failure of myocardium function [82, 83]. In several animal studies, changes in ECG parameters such as the T wave, ST segment and QT interval are highly correlated with cardiac response during hypoxia. Shortening of the QT interval is linked with intrapartum hypoxia and metabolic acidosis and results in an abnormal ST waveform pattern. ST waveform elevation may be an indication of depleting myocardial glycogen reserves with a gradual increase in the severity of hypoxia. A biphasic or negative ST waveform may reflect a situation where the fetus cannot respond to hypoxia and is experiencing myocardial decompensation [28]. A linear relationship exists between the increased amplitude of the T wave and the depletion of myocardial glycogen due to hypoxia. This relationship can be quantified by the ratio of T wave amplitude to QRS complex amplitude [84].

3.4.3. Autonomic nervous system response

The major component of fetal protective adaptations towards hypoxia is the autonomic nervous system (ANS). ANS is composed of the complementary sympathetic and parasympathetic nervous systems and both these systems exert opposite influences to maintain balanced FHR. ANS regulates the cardiovascular system and fetal heart rate via baroreceptors and chemoreceptors [85]. Baroreceptors are sensitive to fetal systematic blood pressure while chemoreceptors are sensitive to pO_2, pCO_2, and pH. For example, in the case of hypoxia, the parasympathetic system is activated by chemoreceptors resulting that can be seen as of late decelerations in the FHR pattern [86]. Sympathetic neurotransmitters and related hormones such as epinephrine collectively belong to the catecholamine family. The secretion of catecholamines plays an important role in the overall regulation of cardiac output function and myocardial glycogenolysis, with stored glycogen in the heart converted to glucose. This compensatory metabolic mechanism alleviates the effects of moderate hypoxia by increasing supplies of metabolic fuel and fetal heart rate and is highly correlated with gestational age and fetal growth. The surge in catecholamines in a mature fetus increases the FHR and can cause changes in the ST segment of the fetal ECG. An immature fetus does not react to catecholamines such as epinephrine, and hence the changes in fetal ECG are not noticeable until severe hypoxia is induced [49].

3.4.4. Hematological response

During mild and moderately severe hypoxia the fetus may maintain oxygen levels despite low blood oxygen tension because of a high concentration of fetal haemoglobin, and the affinity of fetal haemoglobin for oxygen [87]. A haematological effect due to fetal hypoxia is the stimulation of the hematopoietic system to release increased amounts of the hormone erythropoietin (EPO), promoting RBC synthesis [88]. This activation of RBC synthesis is an attempt to increase the oxygen-carrying capacity, and indeed often RBCs are moved into circulation before being fully developed to maximize this effect. The asphyxiated (severely hypoxic) fetus will feature a high level of these immature and nucleated RBCs (reticulocytes). The functionality of the fetal hematopoietic system and response depends on the condition of the fetus and mother. For example, a growth-restricted fetus may not have enough time to respond to hypoxia due to low metabolic reserves even at the initial stages of fetal hypoxia. Other factors associated with increased levels of immature erythrocytes include maternal and gestational diabetes, increased body mass, steroids, and drugs used by mothers for hypertensive treatment [89–91]. Also, the study of Rezaeea *et al* demonstrated that failure of this response is linked with ECG waveform changes including T-wave inversion and ST-segment depression which are highly correlated with a decrease in EPO levels [92].

During hypoxia, when a fetus is deprived of oxygen, the fetus tries to adapt to several defensive

responses to minimize the risk of adverse outcomes. These adaptations and compensatory responses can be detected by parameters such as ECG waveform changes. Also, these responses can be captured by measuring different biomarkers, particularly those involved in acid–base balance, and blood gases. These biomarkers are now discussed in the next subsection.

3.5. Biomarkers during fetal hypoxia

The previous subsections in section 3 have outlined the aetiology of fetal hypoxia with a categorization based on location, a second categorization based on the speed of onset, a staging based on severity, and a series of fetal compensatory mechanisms. Some of these translate into detectable effects that form the basis of biochemical markers. Hence biochemical markers allow the investigation into the nature of a fetal hypoxic case allowing a more complete analysis and a decision on the need and type of intervention required [93]. In this sub-section, these biomarkers are discussed. In particular, the different types of biomarkers, threshold values, correlation of values to the nature of hypoxia, and diagnostic tools used to measure these biomarkers will be discussed. Most of these biomarkers relate to the phenomenon of acid–base balance. Therefore, the acid–base balance is described first, followed by individual parameters that comprise the acid–base balance. A second important set of closely related biomarkers are blood gases and in particular, metrics related to carbon dioxide and oxygen described at the end of the subsection. Further details on how and when these parameters are used in the monitoring of hypoxia are discussed in section 4.

The acid–base balance refers to mechanisms used by the fetus to maintain a normal pH value in the blood. While the details of the metabolic processes that link biomarkers related to the acid–base balance to hypoxia are beyond the scope of this paper, briefly it follows that a hypoxic state leads to a transition from aerobic to anaerobic metabolism. Anaerobic metabolism leads to the production of biochemicals such as lactic acid with the accumulation of H+ ions, causing a move into metabolic acidosis. The acid–base balance is needed to maintain a normal pH which is necessary for normal metabolic processes and fetal growth [94]. The acid–base balance is assessed by analysis of particular parameters including pH (hydrogen ion concentration, $[H^+]$), buffer base, base deficit/ base excess, and lactate levels [59, 94]. Closely related are carbon dioxide and oxygen blood gas parameters in respiratory acidosis, but there are subtle differences with metabolic acidosis. Also, metabolic acidosis is associated with more harmful consequences for the fetus than respiratory acidosis [95]. Assessment of some or all of these parameters has significant diagnostic power [96]. For example, a fetal arterial blood pH < 7.00, and an arterial base deficit > 12 mmol L^{-1} indicates a state of metabolic acidosis [13]. Low *et al* suggested that during labour, mild hypoxia can be diagnosed by determining fetal oxygen tension using an oxygen-measuring electrode. Diagnosis of the more severe stages, however, requires an acid–base analysis using fetal scalp blood sampling [97]. An analysis of some of the individual parameters that comprise the acid–base balance is now presented, also the values of these parameters are arranged in table 1.

3.5.1. pH

Bretscher and Saling introduced the measurement of fetal blood pH as a biomarker of fetal hypoxia in the intrapartum period. This evaluation is performed by microanalysis of fetal blood samples. During the first stage of labour, change in pH was minimal but during the second stage of labour increased risk of pH < 7.2 could be observed due to increased frequency and intensity of uterine contractions [101]. A fetal blood pH value of between 7.20–7.24 mmol L^{-1} is considered normal, indicating routine labour may proceed. However, a fetal pH $\leqslant 7.19$ indicates metabolic acidosis with immediate delivery indicated, and the condition of the fetus is considered pathological. The pre-pathological also called pre-acidaemia range for fetal pH is between 7.00–7.20, with a recommendation for a repeat of blood analysis every 20–30 min in this stage [93, 95, 101, 102]. Importantly, the risk level of neurological sequelae due to fetal hypoxia can be predicted from fetal blood pH. The optimum arterial pH range where neurological risks are minimal is considered between 7.26 to 7.30. A trend towards adverse fetal neurological outcomes is observed when pH is below 7.10, indicating that despite the logarithmic scale used to calculate pH, small changes in $[H^+]$ levels can cause significant morbidity [42]. While the gold standard for pH measurement is microanalysis of fetal blood samples, less invasive techniques may be feasible. For example, Kubli *et al* found a high correlation between arterial pH and CTG patterns such as late decelerative patterns and the total number of deceleration patterns. These patterns are indicative of intrapartum fetal hypoxia and are highly correlated with metabolic acidosis [102].

3.5.2. Buffer base

Buffer base refers to the sum of key buffer anions such as bicarbonate (HCO_3^-) that act to neutralize excess H^+ ions and maintain a steady pH. The use of buffer base measurement was established in the late 1980s. Long-standing (chronic) hypoxia is characterized by a buffer base of < 34 mmol l^{-1}, and in severe hypoxia, the buffer base measurement is < 20 mmol l^{-1}. A decrease in the buffer base value is associated with an increase in lactate concentrations. Lactate levels in turn correlate to the degree and duration of hypoxia [103].

3.5.3. Base deficit (BD)/base excess (BE)

Base deficit (or base excess) is a biomarker measuring the base buffer reserves of the fetus. The base buffers

Table 1. Biomarkers values during fetal hypoxia.

Fetal condition ↓	Acid-base balance					CO_2 metrics	O_2 metrics	
Biomarkers →	pH		Buffer Base [mmol L^{-1}]	BD[a] = − BE[b] [mmol L^{-1}]	Lactate [mmol L^{-1}]	pCO_2[c] [mmHg]	PaO_2[d] [mmHg]	sO_2[e] [%]
Normal	7.20–7.24	⩾7.25	>38	<8	<6.3	⩽4.1	<42	>20	>30
Pre-pathological	<7.20 & >7.0	7.21–7.24	25–32	⩾ 8	6.3–7.1	4.1–4.8	>42	10–12	<30
Pathological	<7.0	⩽7.20	<34	⩾12	>7.1	⩾4.9	>25	<10	<30 for >10 min
Reference	Chafer-Pericas *et al* 2016 [98]	Cummins *et al* 2018 [5]	Murray *et al* 2007 [59], Nordström *et al* 1998 [95]	Knutzen *et al* 2008 [99] , Chafer-Pericas *et al* 2016 [98]	Iorizzo *et al* 2019 [100]	Cummins *et al* 2018 [5]	Aghoja *et al* 2014 [32]	Turner *et al* 2019 [22]	Gibb *et al* 2008 [39]

[a] Base Deficit.
[b] Base Excess.
[c] Partial pressure of carbon dioxide.
[d] Oxygen arterial pressure.
[e] Oxygen saturation.

control the fetal pH value by neutralizing the excessive concentration of H^+ [93]. The two terms are complimentary with a negative base excess identical to a positive base deficit and vice-versa [93]. There is no complete agreement on what BD value indicates the presence of metabolic acidosis in the fetus [95]. The most commonly used threshold value for BD in the extracellular fluid (BDecf) indicating fetal hypoxia is $\geqslant$ 12 mmol L^{-1}. BDecf measures the metabolic component of acidosis (HCO_3-) independently and defines the respiratory component of metabolic acidosis (i.e., levels of CO_2 and O_2). A persistent increase in CO_2 levels may lead to metabolic acidosis with an increase in BDecf value which is considered an important predictor to measure the metabolic component of acidosis [2, 98].

3.5.4. Lactate

Like BD, no agreed value of lactate concentration is used to define metabolic acidosis. Lactate analysis during intrapartum fetal surveillance was introduced in the 1970s by the sampling of blood from the fetal scalp. Lactate concentration is considered to be a diagnostic parameter equivalent to the fetal pH in the determination of fetal hypoxia and the prediction of short-term neonatal morbidity [105]. Though lactate may be equivalent to pH fetal scalp sampling is highly invasive and has a discontinuous nature so it can only be used in high-risk pregnancies [106]. A lactate level of $\leqslant$4.2 mmol l^{-1} is considered normal. Levels between 4.2 mmol l^{-1} to 4.8 mmol l^{-1} indicate pre-acidaemia and lactate levels >4.8 mmol l^{-1} are indicative of true acidaemia with a need for operative intervention [107].

3.5.5. Carbon dioxide (CO_2) metrics

During labour, intrapartum hypoxia caused by a sudden event such as umbilical cord occlusion or maternal hyperventilation may cause an accumulation of CO_2. This accumulation can result in respiratory acidosis. Without proper management, respiratory acidosis gradually evolves into mixed respiratory and metabolic acidosis and will finally develop into pure metabolic acidosis [93, 108]. If a sudden change is observed in CO_2 levels, more likely, that it will affect the respiratory component of acidosis more than the metabolic component of acidosis. Hence monitoring the partial pressure of CO_2 (pCO_2) is important by using blood gas analysis as it can alert the clinician to an evolving respiratory acidosis. Also, the difference in the partial pressure CO_2 levels between arterial and venous cord samples is referred to as $DpCO_2$. A $DpCO_2$ >25 mmHg is considered a sensitive and specified marker of pulmonary disease, renal dysfunction, cardiac anomalies, and neurological morbidity including hypoxic-ischemic encephalopathy and neonatal seizures [109].

3.5.6. Oxygen (O_2) metrics

The blood gas analysis performed from the fetal scalp during the intrapartum period and immediately after fetal delivery assesses a range of oxygen parameters including partial pressure of oxygen (pO_2) and oxygen saturation (sO_2) in arterial blood. Oxygen saturation is the most useful parameter for fetal monitoring. Other metrics sometimes used such as DsO_2, the difference in oxygen between venous and arterial blood samples, is not a sensitive acid–base indicator, with its limited diagnostic value [110].

Hence, there are several biomarkers to assess fetal hypoxia, but none is perhaps regarded as a gold-standard parameter. In some studies as well as in clinical practice pH is considered a significant and relatively robust biomarker with a strong association with FHR patterns [32, 102, 111, 112]. Also, all these biomarkers are related to each other with a change in one parameter linked with a change in another parameter. For example, an increasing degree of intrapartum hypoxia will cause both an increase in lactate concentration and a decrease in buffer base value [103]. Severe fetal hypoxia will cause a high accumulation of lactic acid, a large drop in pH, and an increase in the base deficit [104]. Conversely, other biomarkers are of more limited value for example $DpCO_2$ is associated more with disorders of other systems [109], while DsO_2 is limited in evaluating fetal hypoxia [110]. Along with the knowledge of these biomarkers, fetal surveillance can be achieved using monitoring technologies based on biophysical parameters.

4. Existing monitoring technologies

The monitoring of the fetus dates back to the early 19th century when Francois-Isaac, the Mayor of Geneva, auscultated the fetal heart in 1818 [113]. This work was built upon by Viscount de Kergaradec who recognized the clinical potential of fetal heart auscultation and its application in the monitoring of fetal health [113, 114]. Subsequent research confirmed the finding of de Kergaradec and focused on methods to monitor the FHR. Subsequently, the health of the fetus during the intrapartum period was additionally monitored using techniques such as monitoring of the pulse from presenting parts such as the head, foot, or umbilical cord, and early passage of meconium. These techniques were highly invasive and carried the risk of infection [114].

Today, FHR monitoring remains the gold standard for intrapartum assessment of the fetus [115–117]. FHR monitoring is considered sensitive but not specific for detecting compromises in the health of the fetus. Some fetal monitoring technologies, notably CTG, are frequently used in clinical practice to assess fetal hypoxia. However different monitoring technologies are in existence that can be considered alternatives and adjuncts to technologies such as ST-Analysis (STAN) is used as an adjunct to CTG [118, 119]. The performance of commonly used existing monitoring technologies is described in

Table 2. Performance of existing technologies to detect fetal hypoxia.

Performance →	Sensitivity %	Specificity %	PPV[i]%	NPV[j]%	Cut-off Value	References
Technologies ↓	(95% CI[g])	(95% CI)	(95% CI)	(95% CI)		
FSBS[a]	72	53	57	43	pH $\leqslant$ 7.20	A. Bakr *et al* 2005 [123]
FPO[b]	61.5	96.5	80	90.7	$SpO_2 \leqslant 30\%$	E. Morais *et al* 1999 [124]
FPO	75	49	61	39	$SpO_2 \leqslant 30\%$	A.Bakr *et al* 2005 [123]
FPO	60	31	65	35	$SpO_2 \leqslant 40\%$	A.Bakr *et al* 2005 [123]
IA[c]	22	89	32	82	pH < 7.2	D. Goodman *et al* 2019 [3]
US[d]	65	95	83	88	C/P[h] < 1	G.C. Di Renzo *et al* 1992 [125]
CTG[e]	88	75	30	98	pH < 7.15	T. Chung *et al* 1995 [126]
CTG	53	75	35	86	pH < 7.2	P. Resh *et al* 2011 [127]
ECG/STAN[f]	38	83	45	79	pH$\leqslant$7.15	C. Vayssiere *et al* 2007 [128]
ECG/STAN	62.5	79	11	98	pH$\leqslant$7.05	C. Vayssiere *et al* 2007 [128]
ECG/STAN	43	74	8	96	pH < 7.15	K. Dervaitis *et al* 2004 [129]
ECG/STAN	70	95	65	96	pH < 7.10	A. Zwanenburg *et al* 2016 [130]

[a] Fetal Scalp Blood Sampling.
[b] Fetal Pulse Oximetry.
[c] Intermittent Auscultation.
[d] Ultrasound Imaging.
[e] Cardiotocography.
[f] Echocardiography/ST-Analysis.
[g] Confidence Interval.
[h] Cerebroplacental ratio.
[i] Positive Predictive Value.
[j] Negative Predictive Value.

table 2. Each of these technologies has advantages and challenges as will now be described.

These existing fetal monitoring methods can be broadly categorized into biochemical and biophysical methods [8]. Biochemical methods focus on the detection and quantification of biochemicals related to the underlying aetiology, category, and stages of fetal hypoxia as well as the level of fetal compensation [120, 121]. Biophysical methods monitor the physical events that reflect the condition of the fetus and are generally considered minimally invasive [8].

Details of these different monitoring technologies are discussed in the following sub-sections.

4.1. Biochemical-based technologies

Biochemical-based fetal monitoring technologies include those related to the acid–base balance, and blood gas analysis [114]. These markers can be translated into an interpretation of the health of the fetus.

4.1.1. Sampling of biochemical biomarkers

While biophysical-based technologies tend to be non-invasive, the acquiring of biochemical biomarkers which tend to be largely found in the fetal blood often requires more invasive methods of sampling. These are now briefly discussed.

Acid–base balance biomarkers are assessed by percutaneous umbilical cord blood sampling (PUBS; also called cordocentesis) during the antepartum period, by fetal scalp blood sampling (FSBS) during the intrapartum period, and by blood sampling of the umbilical cord segment immediately postpartum. These all are invasive methods. However, some non-invasive methods such as the Fetal Scalp Stimulation Test (FSST) and Vibroacoustic Stimulation Test (VAST) provide adjunct information in assessing the acid–base balance [94]. These tests do not provide a direct evaluation of acid–base biomarkers or FHR patterns. FSST and VAST as simple fetus arousal assessments are perhaps used as a second-line assessment test to evaluate fetal heart rate using handheld Doppler or Pinard stethoscopes. Generally, these tests are performed by stimulating the fetus during the intrapartum period. FSST applies gentle stimulatory pressure on the fetal scalp for about 15 seconds during a vaginal examination, while VAST uses a vibratory sound stimulus continuously for 3–5 seconds applied to the mother's abdominal skin over the fetal head. These stimulations may result in a need to repeat to acid–base assessment or mode of delivery in the case of abnormal CTG patterns [3, 122].

Of note, FSBS is used during the crucial intrapartum period. FSBS can be performed once the cervix is dilated to $\geqslant$ 3cm, and the amniotic sac is ruptured. An amnioscope is placed transvaginally to image the fetal head with blood collection then performed from the fetal scalp for acid–base evaluation. FSBS is indicated for high-risk pregnancy and upon detection of a non-reassuring FHR pattern. The use of FSBS to measure pH requires a larger amount of fetal blood (35–60 μl) as compared to lactate analysis (5 μl) [106, 131, 132]. In routine clinical practice, FSBS is considered an effective method for pH estimation [121]. The use of FSBS has shown considerable merit in monitoring fetal health [18, 133, 134]

and was originally introduced to reduce the false positive rate and level of unnecessary interventions seen with CTG. However, FSBS may have a low positive predictive value in the presence of meconium. E. Chandraharan *et. al* questioned the reproducibility of FSBS by reporting on an analysis comparing paired blood samples collected simultaneously from a given fetus. This analysis showed that 43% of these samples showed significantly different results. Also, in 16% of cases results from these samples suggested different clinical management strategies for the same fetus. This suggests a need for a continuous and accurate intrapartum fetal monitoring method giving reproducible results [135].

4.1.2. Fetal pulse oximetry

Blood gas biomarkers including oxygen matrices are also assessed by blood sampling. However, due to the intermittent and highly invasive nature of FSBS, an alternative approach using fetal pulse oximetry can be considered. Fetal pulse oximetry is a non-invasive modality used specifically to assess oxygen metrics. Pulse oximetry measures the fetal arterial oxygenation state of blood on the differing absorption characteristics of oxygenated and deoxygenated haemoglobin to red and infrared light [136]. An oximetry sensor is placed on the fetal cheek or head once the cervix has dilated to $\geqslant$3 cm [131]. Pulse oximetry can be used to assess sO_2, written as spO_2, and can be correlated to the level and stage of hypoxia. For example, studies have shown that metabolic acidosis is developed if the fetal oxygenation level falls below 30% for $\geqslant$10 min, allowing pulse oximetry to be used to monitor such cases and allow planning of intervention [140]. The less invasive nature of the fetal pulse oximetry for the fetus, as opposed to FSBS, is an obvious advantage. Also, the modality is relatively inexpensive, requires no external calibration, and is sensitive to changes in blood sO_2. However, pulse oximetry is also sensitive to maternal position and fetal presentation [137]. According to the study presented by Bloom *et al* and the Cochrane Review compared the effectiveness of fetal pulse oximetry during labour with other surveillance methods including CTG and concluded that fetal pulse oximetry does not significantly help to reduce the number of caesarean sections, and may inferior to CTG [137, 138].

4.2. Biophysical-based technologies

Biophysical-based fetal monitoring technologies include auscultation, ultrasound imaging, CTG, and electrocardiography (ECG). These can be used intermittently or continuously.

4.2.1. Auscultation

The fetal stethoscope is an instrument specifically designed for listening to fetal heart sounds and in particular the FHR. Related is the Pinard stethoscope which is also used for fetal auscultation. The fetal heart sounds are amplified by the tubular structure of the devices when pressed against the abdomen of the pregnant woman. Such devices have been in use since the 19th century when it was found that changes in FHR patterns such as accelerations and decelerations were associated with fetal distress [8]. The fetal stethoscope is easily available, portable, and low-cost. Therefore, in low-resource settings, and also for low-risk pregnancies, intermittent auscultation (IA) using a fetal stethoscope or Pinard stethoscope is recommended [13]. However, disadvantages include the manual nature of the technology and hence a higher probability of missing subtle but important features related to the sounds of the fetal heart. Hence in higher-income countries, and higher-risk pregnancies, alternative technologies such as ultrasound are recommended [11].

4.2.2. Ultrasound imaging

Ultrasound Imaging (US) uses high-frequency sound waves that can travel through tissues, with a reflection of waves occurring at the boundary between tissues. A probe is placed on the maternal abdominal or vaginal inner wall with the pattern of reflections used to produce an image of the interior called a sonogram. The US is a mature technology with the advantages of being non-invasive and safe. However, the US in obstetrics requires sophisticated equipment and staff training and is, therefore, more commonly seen in high-resource settings [13]. Significantly, the US can be performed simultaneously with both IA but also with continuous fetal monitoring which is recommended in high-risk pregnancies.

In modern clinical practice, Doppler US is frequently performed to assess the flow of blood in vessels such as the uterine artery, fetal middle cerebral artery, ductus venosus, and umbilical artery [139]. The FHR and umbilical cord movements can also be monitored using Doppler US [140]. The ability of Doppler US to assess blood flow is valuable in fetal hypoxia due to associated hemodynamic changes such as the brain-sparing effect. Doppler US is responsive to these hemodynamic changes and can correlate flow patterns in vessels such as the middle cerebral artery and those in the umbilical cord to fetal hypoxia [141–143].

The use of Doppler US is associated with a reduction of caesarean sections and with fewer inductions of labour. Further, the use of Doppler US in high-risk pregnancies is associated with a reduced risk of perinatal deaths [18]. However, Doppler US suffers from a high rate of false positives leading to unnecessary interventions. The use of Doppler US may also be limited in cases of maternal obesity and fetal movements [18]. Moreover, Doppler US does not characterize FHR with a high level of precision and is sensitive to signals from the external environment [144]. Hence the possibility of poor precision and poor signal quality means the technology is not recommended as the

sole monitoring technology used, especially in high-risk pregnancies [18].

4.2.3. Cardiotocography

Cardiotocography (CTG) also known as electronic fetal monitoring (EFM), is a method of monitoring the FHR and fetal heart patterns, as well as uterine contractions [145]. CTG can be used as an intermittent or continuous monitoring technology depending on the risk. Intermittent CTG is recommended for low to medium-risk pregnancies [146] while continuous CTG is recommended for high-risk pregnancies [15]. CTG can also be performed using both external and internal techniques. External CTG monitoring is generally used during the antepartum and intrapartum period by use of a Doppler US transducer placed on the maternal abdominal wall to monitor fetal heart events, and a tocodynamometer used to monitor uterine contractions [147]. Internal monitoring is possible only during the second stage of labour after the rupture of the amniotic membranes and dilation of the cervix. Internal CTG is achieved using fetal scalp electrodes to monitor fetal heart patterns, and an intrauterine pressure catheter to assess uterine contractions [147].

The use and interpretation of CTG are standardized with guidelines produced by respected organizations including FIGO [1], and NICE in the UK [14]. Of these, the FIGO guidelines are considered more favourable due to their easiest implementation in fetal monitoring systems [19].

CTG data on uterine contractions provides information on the duration, frequency, and strength of the contractions [147]. The CTG data of FHR and fetal heart patterns can be used to predict intrapartum fetal hypoxia by a classification of patterns as normal, suspicious, and pathological. This classification system is based on CTG features including the baseline, variability, accelerations, and decelerations in the heart patterns [1]. Such analysis can also be used to detect metabolic acidosis and associated consequences including neurological morbidity and perinatal deaths [16]. The accelerations, and decelerations in the FHR pattern are considered useful in assessing the hypoxia. Accelerations in the FHR pattern are short-term increases in the baseline heart rate, usually lasting for at least 15 seconds and peaking at least ten beats per minute above the baseline. They are indicative of a responsive and well-oxygenated fetus. However, decelerations in the FHR pattern are temporary decreases in the baseline heart rate. They can be categorized into different types, including early, variable, and late decelerations based on their timing relative to uterine contractions [62, 63]. Late decelerations typically occur after the peak of contractions and are indicative of impaired gas exchange, resulting in hypoxemia, hypercapnia, and acidosis. Late decelerations are generally considered a significant sign of intrapartum hypoxia due to their association with uteroplacental insufficiency and fetal acidosis [61]. However, recent studies have raised questions about the historical three-tiered classification of FHR decelerations [61].

The analysis of FHR recordings often relies on subjective visual inspection and the expertise of the clinician. This can lead to variability in interpretation between different observers. Therefore, to minimize potential variability in interpretation between observers, studies have proposed objective quantification parameters that can objectively measure acceleration and deceleration. Bauer *et al* proposed the acceleration (or deceleration) capacity parameter and applied it to identify a mortality predictor after myocardial infarction. Huhn *et al* were the first to utilize a similar method on FHR data, introducing a parameter similar to acceleration capacity for identifying and categorizing Intrauterine Growth Restriction (IUGR) fetuses. They measured the average acceleration (or deceleration) capacity. This parameter quantifies the mean integral of all periodic acceleration-related oscillations in the FHR pattern, providing a more objective measurement of fetal well-being [148]. Since then, several studies have demonstrated the potential of this innovative method in providing insights into the compensatory activation of the ANS in case of fetal distress by quantifying the acceleration (deceleration) capacity of FHR [149–152]. However, further research is warranted before the clinical adoption of acceleration (deceleration) capacity to analyse intrapartum FHR patterns for reliable fetal hypoxia diagnosis.

CTG was developed as a means to detect and monitor fetal hypoxia and to implement effective interventions. For example, CTG can characterize the various FHR patterns with caesarean section indications in the case of non-reassuring FHR [153]. Despite the availability of other monitoring technologies and the possibility of the use of multiple technologies with CTG, continuous CTG has often been considered a standalone standard care in many countries primarily in low- and middle-income countries due to regional and financial restrictions [19–154]. While CTG does indeed supply such important information on the health of the fetus, the technology has limitations. There is a consensus that a normal CTG trace suggests a healthy fetus, with vaginal delivery possible. However, there is no agreement for the management of an abnormal or suspicious trace. Clinicians often differ in opinions regarding the need and nature of intervention in response to such abnormal patterns [155, 156]. Furthermore, the study of Pinas *et al* demonstrated CTG to have a false-positive rate of 60% for fetal hypoxia and a positive predictive value of only 30% [66]. This study showed that CTG could be used for the prediction of hypoxia but it has a high false-positive rate with a lack of improvements in metrics such as the rate of cerebral palsy or perinatal death since the technology was introduced [66]. This low specificity

and high false-positive rate results in unnecessary surgical interventions such as Caesarean sections [157].

The challenges associated with noise in CTG signals significantly impact the quality and reliability of FHR data. Placing the US transducer accurately requires skilled clinicians, which becomes difficult in preterm pregnancies due to the small fetal heart size and the fetus's unrestricted movement within the uterus. Even when a good US signal is obtained, the continuous recording of the fetal heart rate often experiences severe episodes of signal loss due to changes in fetal heart position or displacement of the transducer on the maternal abdomen. These interruptions in the signal may lead to unsuitable data for clinical interpretation [158]. Due to the nature of FHR signal acquisition, various sources of noise can affect its quality, including maternal and fetal movements, electrical equipment, sensor misplacement, and external environmental factors. This noise generally presents itself as missing values or spiky artefacts [159].

EFM was introduced for fetal monitoring during labour, aiming to detect early signs of fetal distress and ensure timely delivery. Although it became widely adopted, being used in 85% of pregnancies, its effectiveness remained controversial due to the considerable rise in caesarean sections and operative vaginal birth. The main challenge lies in the different opinions of obstetricians about the interpretation of FHR patterns due to intra- and interobserver variability leading to present challenges in decision-making related to labour management [160]. Computerized heart rate (FHR) classification systems could provide advantages in fetal monitoring. However, these systems have not been extensively researched and their availability in clinical practice is limited [161]. The existing CTG interpretation guidelines including National Institute of Child and Human Development (NICHD), are derived primarily from experimental observations, and FIGO lack clarity and diagnostic accuracy for FHR classification systems which makes it difficult to implement these guidelines in the automated classification system [162], Bhatia *et al* compared the FIGO and NICE guidelines and reported that despite encouraging findings suggesting the potential for universal adoption of FIGO 2015 guidelines to reduce practice variation and improve interpretation agreement in CTG, there is lack of standardized guidelines. Hence, these findings suggest the need for adjunct or improved monitoring technologies. Specifically, more research is needed to explore the relationship between intervention rates, modes of delivery, and perinatal mortality and morbidity. This additional investigation is necessary to provide clinicians and maternity units with informed decision-making guidance [19].

Addressing the challenges encountered in CTG interpretation involves several potential solutions. Firstly, the exploration and development of emerging classification methods show promise in improving the accuracy and consistency of CTG interpretations [29, 159, 162]. Additionally, during advanced labour stages, a more comprehensive analysis of CTG traces is recommended, including blinded reviews, universal cord gas collection, and a focus on identifying features linked with genuine pathology [163]. Incorporating clinical variables such as gestational age and maternal temperature into classification criteria can enhance precision in CTG classifications [164]. Moreover, extensive research efforts are vital for understanding the long-term consequences of CTG classifications and evaluating the impact of diverse technologies and equipment in different healthcare settings [164]. Lastly, standardized CTG datasets can facilitate both research and clinical practice, ultimately contributing to enhanced accuracy and reliability in fetal monitoring during labour [19, 162]. These proposed solutions aim to address challenges in CTG interpretation and improve its effectiveness.

4.2.4. Electrocardiography

The electrocardiogram (ECG) records the electrical activity of the heart. Discrete parts of the ECG include the P-wave, QRS complex, ST segment, and T-wave, which can be mapped to the events of systole and diastole. A fetal ECG (fECG) is similar to an adult ECG, with fetal hypoxia monitoring possible through ECG waveform analysis [113]. A comparison of some existing non-invasive fetal ECG monitors approved by the Food and Drug Administration (FDA) is given in table 3.

Concerning the monitoring of fetal hypoxia, ST-Analysis (STAN) is a well-known technology based on fECG waveform analysis. During the autonomic nervous system response towards fetal hypoxia, the myocardium induces secretion of catecholamines which activate β-adrenergic receptors. β-adrenergic receptors, an essential component of the sympathetic nervous system, are cell surface receptors on the myocardial cells and play an important role in the overall regulation of cardiac function. The activation of these receptors leads to myocardial glycogenolysis, with stored glycogen in the heart converted to glucose. This process provides extra glucose and energy to increase cardiac output with the release of potassium ions stored within glycogen. The increase in intracellular potassium ions (hyperkalaemia) may give a rise in T-wave, elevation in ST-segment, and an increase in T/QRS ratio that may help to monitor the oxygenation state of the fetus [49].

STAN monitors are used for continuous intrapartum fetal surveillance and characterize ST events such as the T/QRS ratio and the slope of the ST segment to monitor myocardial hypoxia, and hence fetal hypoxia [169]. STAN is usually used in conjunction with CTG. The main objective of STAN is to improve the accuracy and reliability of CTG by identifying fetal hypoxia at an early stage to avoid the incidence of metabolic acidosis and to decrease the risk of an inappropriate obstetric intervention [170].

Table 3. Existing non-invasive fetal-ECG (NI-fECG) monitors to detect fetal hypoxia.

NI-fECG[a] monitors → Specifications ↓	Monica AN24	Novii	Meridian M110	Nemo
FDA Approval	2011	2017	2017	2018
Monitoring Type	Continuous	Continuous	Continuous	Continuous
Signals Acquired	FHR[b], MHR[c] &UC[d] from ECG-style electrodes	FHR & MHR from fECG and mECG[e] + UC from EMG (Electromyographic Monitor)	FHR, MHR &UC from fECG	FHR & MHR from combined ECG-signals (mECG and fECG) & UC from EHG (Electro hysterogram)
Monitoring position	Maternal abdomen	Maternal abdomen	Maternal abdomen	Maternal abdomen
Gestational age (weeks)	>36	>36	⩾37	⩾21
No. of electrodes	A single patch of 5-electrodes	A single patch of 5-electrodes	4-patches of electrodes	A single patch of 6-electrodes
Mobility	Freedom of movement	Freedom of movement	–	Freedom of movement
Strengths	Reliable for obese patients, better interpretability	Reliable for obese patients, waterproof & peel-and-stick design	Reliable for obese patients	Reliable for obese patients
Weakness	Only for singleton pregnancies (Not suitable for Twins), high FP Contractions	Only for singleton pregnancies, Defective Alarms, Device Sensing Problems	Only for singleton pregnancies	Only for singleton pregnancies
References	[165]	[166]	[167]	[168]

[a] Non-invasive fetal ECG.
[b] Fetal Heart Rate.
[c] Maternal Heart Rate.
[d] Uterine Contractions.
[e] Maternal ECG.

The devices used in STAN are identical to those used in CTG with fetal scalp electrodes and a tocodynamometer used for internal and external monitoring, respectively. The difference is the use of an additional reference electrode attached to the thigh of the mother. STAN has ever-increasing evidence for its value in monitoring fetal hypoxia, helping decide on intervention, and improving neonatal outcomes as seen in numerous randomized controlled clinical trials [171–175].

However, STAN is only suitable for use if started in the first stage of labour. Further, STAN is considered an adjunct to CTG, and so reliant to an extent on the use of CTG. Also, of note is that STAN may not detect hypoxia if it has already occurred before STAN monitoring commenced. There are also issues in the case of rapid FHR ($>$ 170 beats per minute), breech presentation, interference from the maternal ECG, and if the ECG signal is not continuous [170].

This section has reviewed existing technologies used in clinical practice for fetal surveillance during labour including those based on biochemical and biophysical parameters. Biochemical methods are used for monitoring the acid–base balance of the fetal blood. These technologies are assessed by PUBS during the antepartum period, by FSBS during the intrapartum period, and by blood sampling of the umbilical cord segment immediately postpartum. However, these all methods are highly invasive and offer low positive predictive agreement in the presence of meconium fluid. Fetal pulse oximetry offers a less invasive solution but it is highly sensitive to fetal and maternal movements [94, 135, 137, 176]. Biophysical-based fetal monitoring technologies include auscultation, ultrasound imaging, cardiotocography, and electrocardiography. IA is not a continuous fetal monitoring method and suffers from high inter- and intra-observability [11]. With the need for continuous fetal surveillance, biophysical technologies including Doppler US and CTG were introduced for the early detection of hypoxia in the second half of the twentieth century [140, 145]. However, Doppler US and CTG suffer from a high rate of false positives leading to unnecessary interventions [177]. These findings suggested the need for adjunct or improved monitoring technologies. ST-Analysis (STAN) monitoring used as an adjunct to CTG is based on fetal ECG waveform analysis and characterizes electrical events related to the cardiac cycle to monitor fetal hypoxia but uses an invasive scalp electrode and cannot be applied without CTG [169].

In high-resource healthcare settings, continuous electronic fetal heart rate monitoring (CTG and STAN) is the standard to monitor fetal well-being during labour. It provides real-time data on fetal heart rate and contractions and is considered highly effective at identifying fetal distress. However, it comes with significant costs for equipment and maintenance and requires specialized expertise for accurate interpretation [170, 178]. In contrast, healthcare facilities in low-resource settings often rely on intermittent auscultation (IA) with devices like fetal stethoscopes or handheld Dopplers for fetal monitoring. IA is a simpler and cost-effective method but may not offer the same level of accuracy as CTG. It requires extensive training and regular interaction between healthcare providers and patients [3, 13].

The choice of the most suitable technology for early detection of fetal hypoxia may vary depending on the healthcare setting. Ongoing research is exploring alternative technologies and approaches to bridge the gap between different healthcare settings and improve early detection of fetal distress. One promising option is the fetal scalp stimulation test (FSST), which can be performed using IA with a handheld fetal Doppler. FSST shows potential in monitoring fetal oxygen levels, particularly in healthcare setups with limited resources and a high risk of fetal distress [3].

The review of existing monitoring technologies concludes that while all have merit and value for use in clinical practice, there are challenges such as high false-positive rates and lack of specificity of even modern electronic fetal monitoring technology. Although CTG (or EFM) is the most common fetal monitoring technique to assess fetal hypoxia, however, due to inter-and intra-observer error, EFM is still not considered a gold standard technique in clinical settings. A possible solution to overcome the limitations of electronic fetal monitoring is the computerized and automated EFM analysis [179]. An efficient automated EFM system involves several steps including pre-processing of the recorded signal, features selection, and classification techniques for the prediction of fetal hypoxia. The computational and machine learning algorithms are also required to improve the efficiency of automated EFM analysis which will be discussed in the next section.

5. Computational algorithms for electronic fetal monitoring

5.1. Signal pre-processing

CTG and Doppler ultrasonography monitor average FHR, however, FHR can be identified with high accuracy by analysing the fECG [180]. Additionally, analysing the characteristics of fECG provides much more information on the fetus's health status and helps to decide on clinical interventions much more reliably [181]. The fECG can be recorded invasively by placing the electrode on the fetus's head during the second stage of labour [182] or non-invasively by placing the electrode on the maternal abdomen as described in table 3. Invasive (internal) monitoring provides accurate readings that signal can be used as a reference signal for non-invasive (external) monitoring. The recorded signal obtained from internal monitoring is less affected by most of the motion artefacts including maternal cardiac signal and uterine contractions [183]. Assessing fetal hypoxia using invasive fECG involves less computational time due to

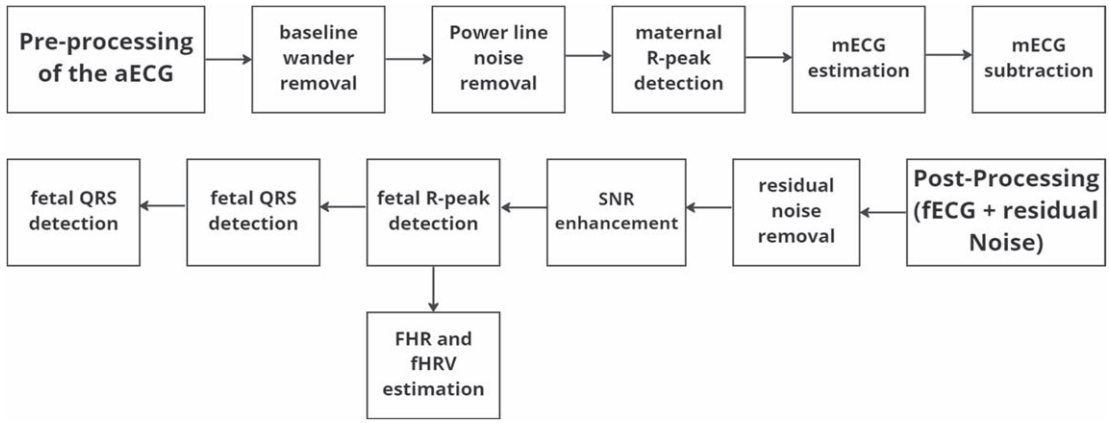

Figure 6. Block diagram for the extraction of fECG from aECG [186].

the absence of major motion artefacts [184]. Compared to non-invasive fECG, Invasive fECG is a stressful and uncomfortable procedure that necessitates rupturing the membranes during labour, exposing both the mother and the fetus to risk for infection [182]. These limitations can be overcome by using non-invasive fECG by acquiring maternal abdominal ECG (aECG). However, aECG is recorded with several types of noises including powerline interference, motion artifacts, and, maternal ECG (mECG) [185]. Hence, extraction of fECG from abdominal signals requires robust signal processing and noise removal techniques. After the pre-processing step of fECG to remove baseline drift, powerline noise interface, and maternal ECG the key steps of prediction of hypoxia from both invasive or non-invasive fECG include fECG features (morphological, frequency-based, and time-based) extraction, features selection and features classification [184]. The extraction of fECG from aECG has been displayed in the block diagram as in figure 6.

Abdominal ECG can be recorded from a single channel or multichannel sources and can be processed to extract fECG using adaptive or non-adaptive methods [182] as displayed in figure 7.

Adaptive methods are developed on learning systems and require at least two signals which are aECG and chest signal. Adaptive methods work on the assumption that chest signal and aECG contain the same noise and are well suited for the cancellation of mECG which is the main artefact in the abdominal signal [28]. The extraction of fECG using an adaptive noise canceller has been depicted in figure 8. Adaptive filtering techniques can be categorized into linear, non-linear, and Kalman filtering techniques. Non-linear filtering further includes Artificial Neural networks (ANN), machine learning (ML), and Extreme Machine Learning (ELM) [180].

In the non-adaptive methods, an unwanted and noisy signal is eliminated to extract the fECG without the need for system adaption. The non-adaptive methods do not require the maternal chest signals and only need aECG to work with constant coefficient values as depicted in figure 9. The non-adaptive methods are accurate and take less computational time than adaptive systems, however, their primary disadvantage is that they are time-invariant in nature [190].

The non-adaptive methods either use single-channel signal sources or multichannel signal sources, which are implemented by numerous methodologies as described in [187]. Although, a separate non-adaptive method works well for each type of signal. However, non-adaptive signal processing methods that are most frequently published include wavelet transformations, independent component analysis, and principal component analysis. These methods offer good computing speed and accuracy [187].

5.2. Features extraction

The filtering algorithms (discussed in section 5.1) remove the primary artefacts, primarily the maternal ECG signal, to extract the fECG. However, these algorithms cannot calculate FHR and other ECG characteristics to diagnose fetal hypoxia. FHR can be calculated using (1) where R_p is the R-peak in the ECG waveform and F_s is the sampling frequency.

$$FHR = \frac{60}{RR_{interval(s)}} = \frac{60F_s}{R_{p(i)} - R_{p(i)}} \quad (1)$$

So, finding the locations of the R-peaks is the main challenge [192]. Pan-Tompkins algorithm can be used to detect the R-peak locations. Agostinelli *et al* applied the standard Pan-Tompkins algorithm on the fECG database described in [193] and compared the results with the modified algorithm known as the improved fetal Pan-Tomkins algorithm (IFPTA). They also computed the value of QRS complex, fHR, and heart rate variability (HRV) using R-peak values. The experimental results evaluated that IFPTA performed better than the standard Pan-Tompkins algorithm [194]. Costa *et al* also used the modified pan-Tompkins algorithm (IFPTA) for the detection of fetal R-peaks [192].

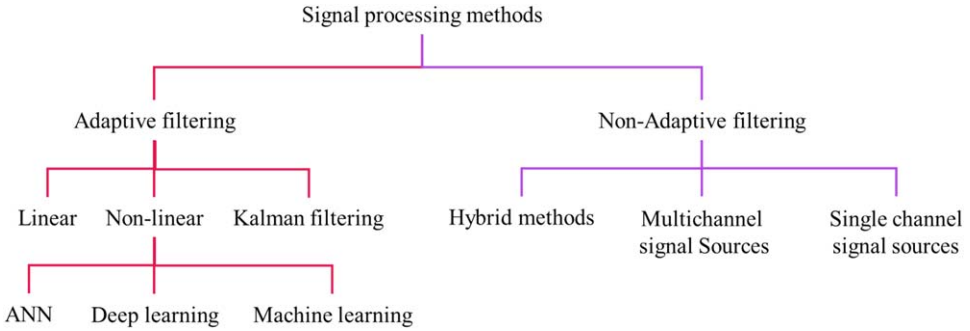

Figure 7. Signal Processing methods for the extraction of fECG [180, 182, 187].

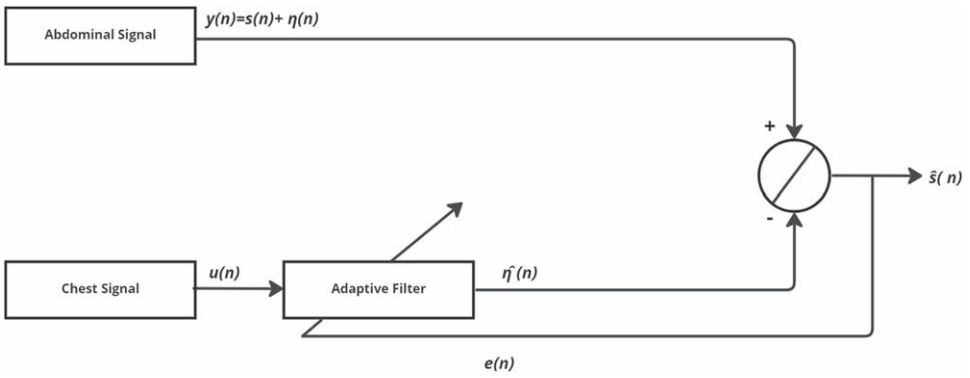

Figure 8. The Block Diagram of Adaptive Noise Canceller to extract fECG. Reproduced from [188, 189], with permission from Springer Nature.

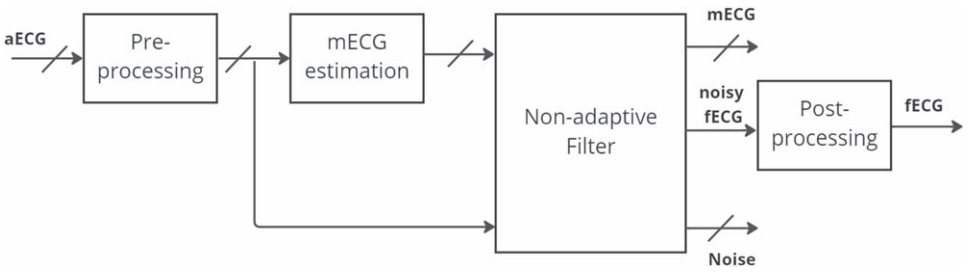

Figure 9. The Block Diagram of Non-adaptive filtering to extract fECG. © [2011] IEEE. Reprinted, with permission, from [191].

5.3. Classification and performance evaluation

Fetal hypoxia can be predicted through the visualization of recorded signals derived from electronic fetal monitoring devices. American College of Obstetricians and Gynaecologists (ACOG) and FIGO guidelines have also defined the morphological features to categorize fetal health status. However, these categorization systems are not accurate. Hence, the inter-observer error between the clinicians and lack of accuracy in the visual representation of the EFM recordings necessitates modelling the EFM recordings using artificial intelligence, computational, and machine learning algorithms to classify fetus health status and predict fetal hypoxia. Although signal processing algorithms have successfully extracted various features from FHR patterns and EFM recordings, machine learning algorithms have further improved the computational efficiency and the prediction of fetal hypoxia through feature minimisation and feature selection.

Celin *et al* used the four machine learning algorithms to classify the ECG signal for the MIT-BIH database. ECG signals were classified using a support vector machine, ada-boost, artificial neural networks, and Naive Bayes algorithms [195]. Spilka *et al* also used SVM to classify intrapartum FHR and concluded that the support vector machine is an efficient kernel-based supervised machine learning algorithm to classify fetal hypoxia [196, 197].

For feature selection to identify FHR in the intrapartum CTG database, Cömert *et al* used two wrapper algorithms, backward elimination (BE) and recursive

feature elimination (RFE), as well as three filters weighted by SVM, information gain ratio (IGR) and relief. Feature selection methods using filters were implemented with 10-fold cross-validation. Then, four classification machine learning algorithms were applied to the selected features. These classifiers are artificial neural network (ANN), k-nearest neighbor (KNN), and support vector machine. They concluded that a combination of the weighted SVM and SVM classifier outperforms the other combination of feature selection and classification algorithms [179]. Another study focused on a new method for the classification of fetal health status using CTG recordings. They used a combination of SVMs and the AlexNet architecture to improve computational efficiency while maintaining high accuracy. The results showed that the proposed model performed better than other classification algorithms, including SVM, multi-layer perceptron (MLP), and deep neural networks (DNN), achieving an accuracy of 99.72%. Additionally, transfer learning was used to speed up training and reduce computational complexity [198].

Comert *et al* used a combination of five machine-learning techniques to classify the FHR classification into normal and hypoxic classes. They compared five different techniques such as artificial neural network, extreme machine learning (ELM), radial basis function network (RBFN), random forest (RF), and support vector machine. The performance of all these algorithms was evaluated using the performance matrix's sensitivity, specificity, geometric mean, F-measure, and training time. Other than training time, all the performance matrices were derived from the confusion matrix. They concluded that all these machine learning techniques provide satisfactory results. However, the artificial neural network performed better results with a sensitivity of 99.73% and specificity of 97.94%. RBFN offered the least training time 0.073 seconds as compared to the ANN 2.236 seconds [197].

For features extracted from CTG recordings, Escaño *et al* compared the traditional classification model (logistic regression model: LRM) with the machine learning algorithms (random forest: RF and neural network (NN)) and evaluated the models using the receiver operating characteristics (ROC) curve. From the experiment results, they concluded that machine learning models perform better as compared to traditional ones. The RF and NN produced quite efficient results with AUC values of 0.865 and 0.857 for validation data (confidence interval: CI 95%) as compared to the LRM (AUC value = 0.840 and CI = 95%) [199].

The use of fuzzy inference systems in predicting fetal distress based on fetal heart rate has been explored in various studies. Skinner *et al* introduced a fuzzy system-based classifier that categorised CTG segments as normal, intermediate, abnormal, or severely abnormal [200]. Similarly, Huang *et al* developed a monitoring system based on fuzzy inference for diagnosing non-reassuring fetal status using FHR and uterine pressure data [201]. Czabanski *et al* employed a two-step analysis of the fetal heart to predict fetal distress. The first step used a Weighted Fuzzy Scoring System based on the clinical interpretation of signals according to FIGO guidelines and the second step involved classification using Lagrangian Support Vector Machines (LSVM) [202, 203]. Ocak *et al* proposed a neuro-fuzzy system, which is a combination of neural networks and fuzzy systems, to predict normal and pathological states based on features extracted from FHR and uterine contractions [204]. In a recent study, Huang *et al* reported an adaptive neuro-fuzzy inference system for antenatal fetal monitoring. The proposed system extracts nine significant features from CTG case data and uses subtractive clustering to determine the number of fuzzy rules. Then self-learning mechanism of neural networks was utilized to initialize and adjust the fuzzy system. The proposed model outperformed existing state-of-the-art antenatal fetal monitoring models. These studies indicate the potential of fuzzy systems to predict fetal distress based on CTG data [205].

There is a clinical need for new approaches to monitor the fetus and detect fetal hypoxia as no current technology is perfect. Since electronic fetal monitoring makes significant use of computational algorithms to predict outcomes, there is a potential for the improvement of computational algorithms, particularly in fECG where fECG waveform carries much more information than simply information about heartbeats. Thus, new ways of extracting and interpreting this useful information using novel or improved computation algorithms improve false positives and the lack of specificity of electronic fetal monitoring technology. This highlights that there is a need for new approaches to monitor the fetus and detect fetal hypoxia. The next section considers what characteristics might constitute such a theoretical ideal monitoring technology.

6. Characteristics of an ideal fetal monitoring technology

While there is an agreement that fetal monitoring is essential, particularly during the intrapartum period to improve fetal and maternal outcomes, there is no ideal fetal monitoring technology in existence [206]. Challenges exist in all the fetal monitoring technologies currently used, introducing the risk of adverse events or unnecessary interventions to the fetus or mother [19]. The standard monitoring technology is considered to be CTG [15]. The issues related to CTG have been already discussed. It may be possible to develop existing technologies such as CTG to iteratively render them closer to ideal, or indeed introduce a range of complementary technologies which when operating in parallel approach an ideal technology.

Bhatia *et al* described an ideal technology as one with high sensitivity, high specificity, user-friendly,

effective in all cases but especially in high-risk pregnancies, and has high reproducibility [19]. Cummins *et al* described the characteristics of an ideal technology for detecting and monitoring intrapartum fetal hypoxia as being:

- Minimally invasive
- Compatible with other monitoring technologies
- Provide accurate readings
- Robust to changes in the external environment such as fetal or maternal movements, and changes in the temperature or pH of fluids
- Capable of collecting a variety of biological fluids not limited to blood
- Capable of performing continuous monitoring [5].

According to Melin *et al,* an ideal fetal monitor should be capable of detecting and monitoring the early stages of hypoxia and providing information on a progressively worsening case. Such timely and precise information using, for example, fetal ECG waveform analysis would help to reduce the number of unnecessary operative interventions [207].

Ignatov *et al* argue the need for a role for computer-assisted decision support in fetal monitoring technologies, as well as a need for general improvement in clinical guidelines [208]. Belfort *et al* further support this enhanced role for computers and artificial intelligence in fetal monitoring noting the generally superior ability of computers to analyse complex patterns that could be applied to data such as that generated from CTG and ECG [209].

Frey *et al* believed that advanced research on electronic fetal monitoring techniques and focused education with appropriate training will help to make accurate clinical decisions before delivery and will help to reduce the rate of intrapartum hypoxic events and neurological encephalopathy [210].

From the aforementioned existing monitoring technologies to determine hypoxia, the biochemical methods are diagnostic and accurate, however, these methods are highly invasive, and they may pose a serious risk to the fetus. The authors believe that the non-invasive biophysical methods are the best screening techniques available and are close to the ideal monitoring system. However, a potential solution to increase the specificity and accuracy of these methods is to improve the quality and reception of the fECG signals and introduce advanced machine learning tools to predict the biochemical markers using the recordings of these biophysical methods. Regardless of the form, such an ideal technology would take the ultimate goal is a reduction in inappropriate obstetric interventions and better outcomes for mother and child. Research in the area of fetal monitoring is active which may result in improved systems. Some of these emerging technologies are discussed next.

7. Emerging sensing technologies

Several novel monitoring technologies and improvements to existing technologies are now discussed. In common with the existing technologies, these systems are based on biophysical or biochemical events that can be related to fetal hypoxia.

The hemodynamic changes that form part of the cardiac response of the fetus to hypoxia are significant predictors of hypoxia in animal studies [211, 212], with similar diagnostic potential in humans in the last gestational period also identified in some studies [213, 214]. These changes may be detectable using imaging modalities such as magnetic resonance imaging (MRI). Traditional MRI is not suitable due to signal interference as a result of factors such as the small size of the fetal heart, high fetal heart rate, and unpredictable distortions due to maternal and fetal movements [215]. However, a novel non-invasive MRI approach to monitoring fetal hemodynamic changes has been developed in ovine models that might be helpful in imaging redistribution of blood and oxygen contents at the initial stage of fetal compromise due to hypoxia [216]. However, MRI is not suitable for continuous monitoring, and large clinical trials are required to study its biological risks for the fetus [217].

Circulating placental RNA (cpRNA) is a potential novel biochemical biomarker to determine fetal hypoxia. Rapid changes in maternal cpRNA are associated with changes in fetal oxygenation levels during the intrapartum period, and while moving through the stages of hypoxia. However, further clinical studies are required to validate these observations and to characterize the association if present. Nevertheless, cpRNA could represent a new biomarker for intrapartum hypoxia [218]. Further, studies have shown an association between the levels of placental-origin microRNAs (including miR-210, miR-21, miR-373, miR-424, and miR-20b) in maternal blood and the different types and stages of fetal hypoxia [219, 220]. Whitehead *et al* performed a study to determine fetal hypoxia non-invasively by measuring circulating miRNA in maternal blood. This study demonstrated that during the intrapartum period, the combined expression of miR-21 and miR-20b was upregulated three-fold in the hypoxic fetus [219].

Fetal distress and progressive development of fetal hypoxia feature oxidative stress which results in the imbalanced production of reactive oxygen species. These oxygen radicals have the potential to damage fetal tissues. Antioxidants such as thiols neutralize oxygen radicals by a redox reaction, which forms a disulphide bond. Hence these thiol antioxidants protect fetal tissues. Studies have identified the change in thiol/disulphide levels during gradually progressing hypoxia.

Hence measurement of this thiol balance may have the potential for use in monitoring fetal hypoxia [221, 222].

During fetal hypoxia, fHRV and FHR decelerations are complicated by the parasympathetic nervous system. Parasympathetic nervous system activity is increased with the gradually developing hypoxia and hence with the increase of metabolic acidosis. Ghesquière *et al* developed an experimental protocol in a fetal sheep model, a new HRV index, and the fetal stress index (FSI) which is highly sensitive to detect fluctuations in parasympathetic nervous system activity and hence may be used to predict fetal hypoxia and acidosis [85].

CTG, as described, is possibly the most commonly used monitoring technology and has been the focus of research seeking to improve the modality. For example, Balayla *et al* have proposed a new algorithm termed FETAL (Fourier Evaluation of Tracings and Acidosis in Labour) in which discrete Fourier transform analysis is applied to FHR tracings with the spectral frequency distribution of the fetal heart rhythm derived. These distributions can then be correlated to fetal pH values and the acid–base balance of the fetus. Thus, according to Balayla *et al*, this technique may provide a novel non-invasive predictor of intrapartum hypoxia with better specificity and sensitivity. However, this method is not in clinical practice and needs more investigation before clinical application [223]. A second novel algorithm based on feature selection has been proposed by Comert *et al* where image-based time-frequency is applied to FHR signals with improved classification accuracy reported [184].

In terms of fECG investigations have been made into the use of internal electrodes to improve the signal from the fetus. The more reliable and accurate signal achieved from the placement of electrodes on the fetal scalp as opposed to the maternal abdomen comes at the trade-off between a non-invasive and invasive approach. However, Martinek *et al* established a relationship between the placement of electrodes on the maternal abdomen and optimized control parameters for the use of adaptive filters. A novel hybrid algorithm for non-invasive fECG signal extraction using these adaptive filters was developed. Optimizing and obtaining high-quality and more accurate fECG signals [224]. Besides, Martinek *et al* have introduced fECG signal processing techniques to measure fetal heart rate variability (fHRV) and assess information from the ST events. The researchers introduced a novel approach for the statistical analysis of real-time data using a fetal scalp electrode signal as a reference with real-time data collected by placing several electrodes on the maternal abdomen [84].

8. Conclusion and next steps

Intrapartum fetal hypoxia remains a leading cause of stillbirths, neonatal deaths, and significant morbidity such as long-term neurological sequelae primarily in low-resource settings. The origin of fetal hypoxia is attributed to various conditions and causes interlinked to the mother, placenta, and fetus. Intrapartum fetal hypoxia can be further categorized depending upon the speed of onset and duration of hypoxia i.e., acute hypoxia (sudden fetal oxygen deficiency lasting >3 min), subacute hypoxia (persisting for 30–60 min), gradually developing hypoxia (developing over several hours), and chronic hypoxia (developing during pregnancy period). During intrapartum hypoxia, the fetus may experience three sequential stages of oxygen depletion. These stages include mild hypoxia (hypoxemia), followed by moderately severe hypoxia, and finally severe hypoxia (asphyxia).

Fetal compensatory mechanisms exist as means to try to maintain homeostasis in the face of hypoxic insult. During labour, the state of these compensatory mechanisms depends on the stage of hypoxia as well as the duration, frequency, and intensity of hypoxia-inducing events, and the physiological reserves of the fetus. Even during normal labour, the fetal defence mechanisms deal with a deprivation of oxygen caused by the reduction of blood as a consequence of uterine contractions. In mild hypoxia, the fetus tries to adapt by slowing the FHR (bradycardia) and thus minimizing the demand of the myocardial tissue for oxygen. In moderately severe hypoxia redistribution of blood occurs to the vital organs such as the brain, heart, and adrenal glands, at the expense of peripheral tissues with a gradually increasing FHR seen as slight tachycardia. The final stage of asphyxia features a move from aerobic metabolism into anaerobic metabolism with consequent metabolic acidosis and a high risk of fetus morbidity.

The main purpose of intrapartum fetal surveillance is to prevent stillbirths and neonatal deaths as well as to prevent unnecessary obstetric interventions. Therefore, all fetal monitoring technologies should indicate the degree of fetal hypoxia and information related to the acid–base balance. Indeed, fetal hypoxia can be detected and monitored using biomarkers related primarily to the acid–base balance. Of these biomarkers, pH has been considered the most reliable predictor of fetal hypoxia. Fetal monitoring technologies based on biophysical parameters may also be used including auscultation and CTG. Auscultation techniques such as IA are used for low-risk pregnancies, while for high-risk pregnancies CTG is the most common technique in clinical routine practice. CTG monitors FHR, FHR pattern, and UC and can indicate fetal hypoxia, but the technology has low specificity and a high false-positive rate resulting in unnecessary surgical interventions.

Electronic fetal monitoring still has challenges due to poor interpretation of the FHR patterns and underperforms due to inter- and intra-observer errors. To overcome these limitations computational machine learning algorithms have been discussed for automated CTG systems to predict fetal hypoxia. However, a compromise between the computational cost for

each machine learning algorithm primarily for fetal hypoxia monitoring, and their performance is another challenge that would be assessed in future research.

There is a global consensus that some form of fetal monitoring should be used during intrapartum care to reduce adverse maternal and fetal outcomes. However, existing monitoring technologies are inadequate, invasive, and time-consuming leading to the conclusion that there is a requirement for continuous, accurate, and non-invasive monitoring to fulfil the need for intrapartum fetal monitoring in clinical practices.

In this article, the main features of an ideal fetal monitoring technology are presented. An ideal monitoring technology should have features such as high sensitivity, high specificity, and high reproducibility. The ideal technology should be minimally invasive with continuous monitoring and detection of fetal hypoxia possible at an early stage of hypoxia and with high precision of detection.

Given the high false-positive rate and lack of specificity of electronic FHR monitoring technology, even with the use of adjunct technologies, challenges exist with fetal monitoring methods used in routine clinical practice. This indicates that there is a need for new approaches and innovations to successfully monitor fetal hypoxia. Based on the biophysical and biochemical events during fetal hypoxia, some novel technologies based on hemodynamic changes, circulating placental RNA, and thiol/ disulphide levels are under active development. However extensive research and clinical studies are still required to validate these emergent technologies before they may be seen in clinical use.

However, there is an evident ongoing need for further research to identify new diagnostic parameters and advance new monitoring technologies for the prediction and effective treatment of fetal hypoxia.

Data availability statement

No new data were created or analysed in this study.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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