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Manuscript title: Methods for Monitoring Risk of Hypoxic Damage in Fetal and Neonatal Brains: A Review

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Abstract

Fetal, perinatal, and neonatal asphyxia are vital health issues for the most vulnerable groups in human beings, including fetuses, newborns, and infants. Severe reduction in oxygen and blood supply to the fetal brain can cause hypoxic-ischemic encephalopathy, leading to long-term neurological disorders, including mental impairment and cerebral palsy. Such neurological disorders are major healthcare concerns. Therefore, there has been a continuous effort to develop clinically useful diagnostic tools for accurately and quantitatively measuring and monitoring blood and oxygen supply to the fetal and neonatal brain to avoid severe consequences of asphyxia Hypoxic-Ischemic Encephalopathy (HIE) and Neonatal Encephalopathy (NE). Major diagnostic

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technologies used for this purpose include fetal heart rate monitoring (FHRM), fetus scalp blood sampling (FBS), ultrasound (US) imaging, magnetic resonance imaging (MRI), x-ray computed tomography (CT), and nuclear medicine. In addition, given the limitations and shortcomings of traditional diagnostic methods, emerging technologies such as near-infrared spectroscopy (NIRS) and photoacoustic (PA) imaging have also been introduced as stand-alone or complementary solutions to address this critical gap in fetal and neonatal care. This review provides a thorough overview of the traditional and emerging technologies for monitoring fetal and neonatal brain oxygenation status and describes their clinical utility, performance, advantages, and disadvantages.

Keywords

Fetal and Neonatal; Blood flow; Oxygenation; Hypoxic-Ischemic; Neonatal Encephalopathy; Diagnostic Imaging; Ultrasound; Photoacoustic; MRI; X-Ray CT

Introduction

Perinatal asphyxia, or oxygen deprivation, is believed to cause approximately 23% of newborn deaths globally [1–4]. Furthermore, a severe reduction in oxygen and blood supply to the fetal brain can cause hypoxic-ischemic encephalopathy (HIE), leading to long-term neurological disorders, including mental impairment and cerebral palsy [5–12]. Such neurological disorders are major healthcare concerns [13–15]. Pregnancy complications, such as prolonged, arrested, and obstructed labor and inadequate use of oxytocin, are some of the major causes of perinatal asphyxia and HIE [1–18]. Neonatal encephalopathy (NE) is a clinical syndrome characterized by disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation. It manifests as a reduced level of consciousness or seizures, often accompanied by difficulty initiating and maintaining respiration and by depression of tone and reflexes [1]. HIE, or birth asphyxia, is one of the leading causes of NE. To date, there is not a gold-standard test for diagnosis of HIE, and it remains challenging to determine whether acute hypoxic-ischemic events contributed to NE. The incidence of NE varies between 2 and 9 per 1000 term births [2, 3]. In a 2010 comprehensive review, the estimated incidence of NE was 3.0 per 1000 live births (95% CI 2.7–3.3), while the estimated incidence of HIE (a subset of NE) was between 1.3 and 1.7 per live births (95% CI 1.3–1.7) [4]. It is estimated that 30% of NE cases in developed populations and 60% in developing populations have some evidence of intrapartum hypoxia-ischemia [4]. Newborns presenting with signs of NE warrant immediate clinical assessment to determine eligibility for therapeutic hypothermia, which is typically started within six hours of birth.

During development, the fetus has a significant margin of safety for oxygenation. Physiological adaptation mechanisms include increased affinity of fetal hemoglobin to oxygen, increased basal blood flow to most tissues, and release of oxygen to the fetal tissues at a lower oxygen tension [5–7]. Acute hypoxia in late gestation fetuses leads to decreased fetal breathing movements and decreased heart rate (bradycardia), leading to less oxygen consumption, as one of the fetal defense mechanisms [8]. Bradycardia allows cardiac output and perfusion pressure maintenance by prolonging cardiac end-diastolic

filling time, increasing end-diastolic volume [9]. Another defense mechanism, known as the fetal brain sparing effect, is explained by the redistribution of blood flow away from peripheral vessels to vital organs, including the brain, heart, adrenal glands, and kidneys. Carotid chemoreflex activation leads to bradycardia through the vagal nerve stimulation and increased peripheral vasoconstriction [10] (Figure Legends Fig. 1). Hormones and local vascular mediators further maintain peripheral vasoconstriction. However, prolonged, and inadequate fetal defense mechanisms trigger a cascade of cellular processes, leading to inflammation, cell death, and subsequent HIE.

Based on a report by the American College of Obstetricians and Gynecologists (ACOG) guidelines for HIE, all of the following conditions should be present for the infant to be considered as having HIE: Apgar score of <5 at 5 minutes and 10 minutes, fetal umbilical artery pH <7.0, or base deficit ≥12 mmol/L, or both, acute brain injury seen on brain MRI or magnetic resonance spectroscopy (MRS) consistent with hypoxia-ischemia, presence of multisystem organ failure consistent with HIE (Fig. 2). Other factors that can introduce a sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery include the ruptured uterus or severe abruptio placentae. Fetal heart rate monitor patterns are consistent with an acute peripartum or intrapartum event, such as a category III pattern. Additionally, the neuroimaging evidence shows a pattern of brain injury typical of hypoxic-ischemic injury in the newborn, including deep nuclear gray matter or watershed zone injury, and no evidence of other factors contributing to the encephalopathy [1]. The National Institute of Child Health and Human Development (NICHD) category III FHR tracing is defined as having either sinusoidal pattern or absent baseline variability plus recurrent late decelerations, recurrent variable decelerations, or bradycardia [19]. Whether neuroimaging or other methods for fetal hypoxia monitoring can sooner or later be used as a gold-standard for diagnosing prenatal hypoxia and hypoxic-ischemic brain injury remains to be established.

Currently, available indicators such as fetal heart rate monitoring (FHRM) and fetal scalp blood sampling (FBS) have certain diagnostic/prognosis limitations [12]. As the gold-standard for diagnosing fetal intolerance of labor, FHRM is most widely used to monitor fetal well-being in obstetrics despite its poor sensitivity. This has led to an increase in operative deliveries [13]. On the other hand, FBS was proposed as a complementary test to increase FHRM specificity to reduce unnecessary interventions. However, FBS was also reported as having a limited contribution to FHRM and for being an invasive procedure only applicable in late stages of labor after rupture of membranes. Currently, its use in high-risk pregnancies is very low (<1.5 to 2%) [14].

For the past decade, the well-accepted and conventional neuroimaging modalities, including cranial ultrasonography (CUS), computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine methods (PET, SPECT), have been the standard of care for evaluating infants with neurological pathology [14–17, 20, 21]. While CUS is widely used for fetal and neonatal brain evaluation, fetal MRI is studied to confirm and characterize brain abnormalities detected by routine CUS. Fetal MRI is not a common tool in practice and is considered when high-quality neurosonography is unavailable or cannot provide specific diagnostic information [22, 23]. Among various neuroimaging modalities for neonatal brain

evaluation, the CUS is the preferred and most widely used modality. It can be used to image the evolution of lesions and brain maturation due to its rapid, safe, and easy technology. The CUS can detect cerebral edema within 24 hours after the hypoxic-ischemic insult and provide findings related to intrapartum hypoxia, i.e., increased echogenicity [16, 17]. The vascular abnormalities (Fig. 3) [24] can be detected by color Doppler sonography (CDS). The CT imaging modality has been rarely used for neonatal brain evaluation due to radiation exposure and reported low sensitivity to detect early, small or infra-tentorial infarcts [20]. Neonatal MRI is a relatively new technique that has rapidly become the study of choice for the evaluation in newborns. It is considered the most sensitive technique to detect early fetal hypoxia [21]. Still, there are some limitations, such as its non-portability and high cost. Nuclear medicine offers non-invasive imaging methods using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to study cerebral perfusion and metabolism. Some significant limitations restrict nuclear medicine use in neonates, including ionizing radiation and high operating cost. Additionally, PET is not accessible as a point of care testing for observation/investigation in patients for a routine checkup or during emergencies. The purpose of this review article is to provide an objective overview of the utility and limitations of existing methods for fetal and neonatal brain hypoxia assessment and to introduce new emerging technologies such as photoacoustic (PA) imaging as a potential technique for monitoring to overcome existing limitations in current practice.

Diagnostic methods for monitoring fetal brain blood flow and oxygenation

I. Fetal Heart Rate Monitor (FHRM)

Fetal Heart Rate Monitor (FHRM) or Cardiotocography (CTG) is an electronic technology for recording the fetal heart rate referenced to the uterine contractions during pregnancy and labor [25]. The technique was introduced as a screening test in the 1960s to improve the detection of fetal hypoxemia and reduce cerebral palsy and perinatal mortality, particularly in high-risk pregnancies [26, 27]. By detecting the pattern changes in the CTG signals, the FHRM system was anticipated to identify signs of fetal hypoxia and suggest cesarean section or instrumental vaginal birth [28, 29]. A value below 110 bpm is considered as bradycardia and above 160 bpm tachycardia. For example, NICHD category III tracing indicates current fetal hypoxia. It is defined as having either sinusoidal pattern or absent baseline variability plus recurrent late decelerations, recurrent variable decelerations, or bradycardia [30].

Several antepartum fetal surveillance techniques based on FHRM are in clinical use. These include the contraction stress test (CST), a nonstress test (NST), biophysical profile (BPP), and modified BPP. The clinical studies suggest that initiating antepartum fetal testing at 32 0/7 weeks of gestation or later is appropriate for most at-risk patients [31–34]. However, in pregnancies with high-risk conditions, testing might begin at an earlier gestational age when delivery would be considered for the perinatal benefit [35–40].

The CST is based on the response of the FHR to uterine contractions. It relies on the hypothesis that uterine contractions will transiently worsen fetal oxygenation. Worsening in oxygenation status will lead to the FHR pattern of late decelerations (Fig. 4c). The NST is

based on the hypothesis that the heart rate of a fetus that is not acidotic or neurologically depressed will temporarily accelerate with fetal movement. Heart rate reactivity is thought to be a good indicator of normal fetal autonomic function. Loss of reactivity is usually associated with a fetal sleep cycle but may result from any cause of central nervous system depression, including fetal acidemia. The BPP consists of an NST combined with four observations made by real-time ultrasonography (fetal breathing movements, body or limb movements, fetal tone, and amniotic fluid volume) [41]. The modified BPP combines the NST, an indicator of fetal acid-base status, with an amniotic fluid volume assessment, as an indicator of long-term placental function [42]. Because antepartum fetal surveillance tests have high false-positive rates and low positive predictive values, abnormal test results are usually followed by another test or delivery based on consideration of test results, maternal and fetal condition, and gestational age [43, 44].

The specificity of FHRM for the prediction of cerebral palsy is low, with a reported false positive rate as high as 99.8% [25], even in the presence of multiple late decelerations or decreased variability (Fig. 4a–c) [45]. Another significant limitation is its inability to assess fetal oxygen status directly [46]. Approximately 30% of fetuses will have a non-reassuring FHR pattern at some time during labor [47]. However, it has been estimated that even the most ominous fetal heart rate patterns are associated with at most a 50% to 65% incidence of neonatal asphyxia or neonatal acidemia [48, 49]. Although some evidence suggests that intrapartum fetal monitoring is associated with a reduction in intrapartum death [50], a reduction in long-term neurologic impairment has not been proven. All available data are derived from trials comparing continuous electronic monitoring with intermittent auscultation. No randomized trials are comparing intrapartum fetal monitoring versus no intrapartum fetal monitoring.

II. Fetal Scalp Blood Sampling (FBS)

Fetal scalp blood sampling (FBS) was introduced for obstetric care in the late 1960s. In the FBS procedure (Fig. 5a), a small blood sample from the fetal scalp is drawn for examination and tested for two constituents: pH and lactate, indicators of acid-base homeostasis [51]. As an ancillary method, FBS is now considered a less useful test for intrapartum fetal evaluation. An amnioscope with a light source is used to expose the fetal scalp, and after puncturing the scalp with 2-mm blade, the blood is collected into capillary tubes. The technical difficulty in obtaining fetal blood samples, especially in morbid obesity patients, is challenging. The test requires that the cervix be dilated at least 2 to 3 cm, and is often uncomfortable for the mother. Rare complications include infection, hemorrhage, and leakage of cerebrospinal fluid [52–56]. Intrapartum pH and lactate measurements have not been clearly proven to reduce emergency cesarean deliveries or operative vaginal births or improve long-term perinatal outcomes [57–59]. Schiermeier et al. (Fig. 5b) [14] evaluated the sensitivity and specificity of intrapartum computerized FIGO criteria for CTG and fetal scalp pH during labor. The study concluded that computerized CTG analysis is highly sensitive for fetal acidosis and can be used as an objective adjunctive criterion during delivery. More recently, the study group performed a multicenter observational study to evaluate the value of FBS as an adjunct test to CTG to predict adverse neonatal outcomes [59]. The primary outcome was the prediction of neonatal acidaemia diagnosed as umbilical

cord arterial pH < 7.05. The secondary outcomes were the prediction of Apgar scores < 7 at 1st and 5th minutes and admission to the neonatal intensive care unit (NICU). As an adjuncts test to CTG, FBS offered limited value to predict neonatal acidaemia, low Apgar scores, and admission to NICU. For this reason and many others, including difficulties with quality control, cost, patient discomfort, sample failure rates up to 10 percent, and unavailability of sampling kits, FBS is performed rarely in the United States and worldwide.

Diagnostic methods for monitoring neonatal brain blood flow and oxygenation

I. Computed Tomography (CT)

Computed Tomography (CT) scan of the head was an imaging technique that uses x-rays and effectively detects hemorrhage with the added advantage of limited sedation need. CT was sometimes used for neuroimaging in neonates with NE despite potential harm from radiation exposure [60, 61]. However, due to the noticeable risk of depositing harmful radiation exposures, CT scans have been abandoned in the past decade [62, 63]. It has also been reported to suffer from low sensitivity and specificity towards a diagnosis of HIE [15, 64, 65]. Given the excessive radiation exposure, fetal CT is not recommended for brain imaging, and in rare cases, the prenatal low-dose CT is used to detect congenital skeletal abnormalities [66]. Multidetector CT can be used for screening intracranial hemorrhage in very sick neonates without the need for sedation or when an MRI is not accessible [67].

Clinical approaches for monitoring both fetal and neonatal brain blood flow and oxygenation

I. Near-Infrared Spectroscopy (NIRS)

Cerebral Near-Infrared Spectroscopy (NIRS) monitoring uses light in the near-infrared spectrum region, which is absorbed by oxygenated and deoxygenated hemoglobin and cytochrome oxidase (CytOx). Total hemoglobin is an index of cerebral blood volume, and cytochrome oxidase is the terminal complex of the mitochondrial respiratory chain and adenosine triphosphate (ATP) [68]. Cerebral oximetry assessed via NIRS has been proposed as a “standard of care”, and this technique is widely used now (Fig. 6) [69, 70]. A major advantage of this technique is that it allows for non-invasive continuous monitoring of cerebral oxygenation.

NIRS can provide data about several important variables of cerebral oxygenation and hemodynamics (Fig. 7) [71]. Since 1985 it has been used as a research tool for investigating the newborn infant’s brain [72]. More recently, the technique has been adapted to monitor the human fetal brain during labor [73]. Commercial continuous-wave NIRS systems have been used in HIE to monitor relative cerebral hemoglobin oxygen saturation (SO_2). OxiFirst® fetal oxygen saturation monitoring system is a new type of fetal monitor that measures oxygen saturation in the fetuses’ blood as a sign of fetal health during labor and delivery [74]. The sensor is inserted into the mother’s uterus and placed against the temple or cheek of the fetus. The monitor displays fetal oxygen saturation as the percentage of oxygen in the blood of the fetus. In a randomized, controlled clinical trial of more than

1,000 births conducted at nine sites throughout the United States, fetal oxygen monitoring proved to be safe and efficient for measuring the oxygenation of a fetus during periods of non-reassuring fetal heart rate patterns [75, 76].

NIRS is an old technique dating back to 1977 used initially as a non-invasive neuroimaging tool that can measure local hemodynamic changes in the brain. NIRS can continuously and simultaneously monitor cerebral, intestinal, and renal perfusion and oxygenation in different organ systems at the bedside without interrupting routine care [77] (Fig. 8). Thus, near-infrared spectroscopy can augment current physiologic monitoring to increase awareness of abnormal perfusion status in the preterm population and potentially reduce risks associated with several diseases that may lead to ischemic injury.

NIRS is a promising technique for fetal hypoxia. Still, its use as a sole diagnostic measure of the balance between the brain oxygen requirement and the brain oxygen supply is still premature. A major problem with NIRS monitoring is that the percentage of arteries, capillaries, and veins mixing in the brain circulation is not constant. In cerebral circulation, arteries are estimated to represent 10–20% of the total vessel volume, capillaries 5%, and veins the remaining 75–85%. Thus, SO_2 predominantly represents the venous saturation in the brain [78]. Another limitation is the influence of hemoglobin values on NIRS monitoring and the effect of pCO_2. In addition, hemodilution, transfusion, hypocapnia, and hypercapnia lead to significant variations in cerebral oximetry [79]. Nevertheless, NIRS has been increasingly used in clinical application, and further studies may widen the fields of application in fetal hypoxia monitoring.

II. Cranial Ultrasound (CUS)

Cranial ultrasound (CUS) is a technique for scanning the brain, and it is used almost exclusively in fetus and neonates because its fontanelle provides an “acoustic window.” The CUS is the preferred modality to image the fetal and neonatal brain for the evolution of lesions and brain maturation due to its rapid and easy technology and safety [80] (Fig. 9). The advantages of the CUS are numerous: it is an effective, non-invasive, and portable method of investigation. Several studies have reported its capability to differentiate hypoxic-ischemic injury from other causes of neonatal encephalopathies, including metabolic diseases [81, 82]. Moreover, color Doppler sonography (CDS) enables the assessment of brain perfusion and its pathology. Thus, the CDS options are essential prerequisites for the modern US – not only for assessing anatomy and patency of major vessels but also for the assessment of flow dynamics and peripheral vasculature, which in several conditions can be the clue to the diagnosis, e.g., asphyxia, brain death, high-pressure hydrocephalus, venous thrombosis.

Several limitations of CUS have been described in the literature, including a small field of view, limited soft-tissue acoustic contrast, beam attenuation by adipose tissue, poor image quality in oligohydramnios, and limited visualization of the posterior fossa in some cases due to variations in the size of the acoustic window, such as at the 33 weeks’ gestation [83–86]. Thus, sonographic findings are occasionally inconclusive or insufficient to guide treatment choices. In addition, the quality of images depends on the skills and experience of the sonographer, as some areas of the brain are challenging to visualize, and several

abnormalities (i.e., coagulation necrosis and colliquative necrosis) remain beyond the scope of its abilities.

Although fetal malformations of the posterior fossa encompass a heterogeneous group of abnormalities, they can have similar characteristics on ultrasound. Therefore, multiplanar ultrasound with high-frequency probes and a transvaginal approach for fetuses in vertex presentation can be beneficial in such circumstances. In addition, when sonographic findings are inconclusive or insufficient to guide treatment choices, fetal MRI can represent a clinically valuable supplement to neurosonography [15, 87, 88]. However, neonatal CUS is not routinely used to predict outcomes in HIE, and it is not as sensitive as fetal magnetic resonance imaging (MRI) in diagnosing brain injury and may take several days to become apparent [22, 23]. Therefore, fetal MRI has become an addition to ultrasound in prenatal diagnosis.

III. Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is an imaging technique based on nuclear magnetic resonance (NMR) science. When placed in an external magnetic field, certain atomic nuclei can absorb and emit radio-frequency energy. In clinical and research MRI, hydrogen atoms are most often used to generate a detectable radio-frequency signal received by antennas near the examined anatomy [89]. Fetal MRI initially emerged as a clinically useful supplement to sonography in the 1980s but was limited due to slow sequences requiring fetal and maternal sedation [90].

While ultrasound has been the primary imaging modality for fetal and neonatal evaluation, MRI has offered multiple advantages over ultrasound in this field [91]. The advantages of using fetal MRI include improved soft-tissue contrast and characterization, a larger field of view, and access to functional data. Multiple modalities of MRI have become available, including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), MR spectroscopy (MRS), and blood oxygenation level-dependent (BOLD) MRI. The latter is highly sensitive to changes in blood oxygenation levels and has been used in the quantitative assessment of cerebral metabolic rate in stroke and multiple sclerosis patients [92, 93]. Conventional MRI images (T1w and T2w), usually performed after day four from delivery, provide information on myelination status and preexisting brain developmental defects. DWI is highly sensitive for areas of edema and allows earlier identification of injury patterns in the first 24–48 hours. Both conventional MRI sequences (T1w and T2w) and DWI have a good specificity (>90%) and positive predictive value (>85%) in predicting death or major disability at age two years [94].

MR imaging of the fetus can be done at both 1.5T and 3.0T field strengths. A major advantage of 3.0T MRI compared to 1.5T is its increased signal-to-noise ratio (basically linearly proportional to the imaging field strength) [91]. The benefits of this increase in signal-t-noise include: (1) higher imaging resolution, (2) improved tissue biochemical profiling through MRS, (3) shorter imaging times and (4) improved functional data. However, to keep susceptibility related artifacts similar to those seen at 1.5T, shorter echo times are required. However, the susceptibility effects can be particularly advantageous when using susceptibility weighted imaging (SWI). Furthermore, unless the sequences are

appropriately redesigned, the operating frequency of 128 MHz of 3.0T MRI will lead to higher radio-frequency energy deposition as measured by specific absorption rate (SAR). Recently, it has been shown that SAR can be kept well within FDA guidelines using modified pulse sequences [95] Some studies using 3T scanners have been reported around the world. Therefore, fetal brain imaging at 3.0T can provide higher resolution and better imaging quality while simultaneously reducing the SAR and can serve as a viable means to image the fetal brain, body and vasculature [91, 96].

BOLD-based signal changes in MR susceptibility-weighted imaging (SWI) have been previously used to evaluate and study stroke in adults and pediatric and neonatal populations [97] (Fig. 10). SWI has also been used to study traumatic brain injury in the pediatric population due to its sensitivity to hemorrhagic lesions. SWI is a high resolution, fully flow compensated MRI technique, which is more sensitive than the typical T2* based BOLD acquisition because of its unique combination of the T2* weighted magnitude data with the phase data [97]. Phase image from gradient-echo sequences like SWI provides distinctive contrast, unlike the conventional T1, T2, and T2* contrast, emphasizing small differences in tissue magnetic susceptibility property. Hence, SWI is particularly useful when differentiating arteries from veins. It is also considered highly sensitive to micro-bleeds or changes in cerebral venous oxygen saturation [98]. During a stroke, an increased oxygen extraction in the tissue with reduced perfusion leads to an increase in deoxyhemoglobin content in the veins, leading to their prominent appearance on SWI [99–101]. In addition, the unusually prominent deep medullary veins are seen in SWI during a hypoxic-ischemic injury in neonates [100].

Visibility of the veins in SWI depends on the phase signature of the venous vasculature, which is a function of blood oxygenation level, blood hematocrit, and the magnetic susceptibility of fetal blood [97]. Physiological variations in hematocrit, cerebral blood flow, and magnetic susceptibility can affect the venous phase and visibility of veins in SWI. Other SWI sequence parameters such as echo time (TE) and image resolution can also influence the visibility of veins: the longer the TE, the better the phase definition within the veins, and the smaller the voxel size, the better the visibility of smaller veins. Moreover, the fetal head orientation relative to the main magnetic field also influences the venous phase in SWI. This problem was overcome by appropriately modulating the phase mask generation step to account for arbitrary head orientation. A linear phase mask with an appropriate sign for enhancing venous vasculature was chosen depending on the sign of the venous phase [97].

Chronic hypoxia is known to be a predictor of abnormal neurodevelopment and cognitive disabilities. Therefore, the fetal cerebral blood oxygenation status could be an important physiological parameter in identifying fetuses at risk of brain injury. Recent works on quantitative MRI have either used the transverse relaxation rate property, T2, of blood or the paramagnetic nature of deoxyhemoglobin (dHb) with MR susceptometry to measure blood oxygenation status in the fetus [102, 103]. The former method was successfully applied in the major vessels of the heart of fetuses of third-trimester, but it was susceptible to radio-frequency field inhomogeneities and was also associated with a high SAR, especially when imaging at 3.0T [103]. The MR susceptometry measures the magnetic susceptibility of blood which is related to the amount of deoxyhemoglobin present.

Quantitative susceptibility mapping (QSM) is a recently developed MRI technique for quantifying the spatial distribution of magnetic susceptibility within biological tissues [104]. QSM uses both the intravascular and extravascular phase to estimate the magnetic susceptibility on a pixel-by-pixel basis. QSM is independent of the orientation and the shape/size of the structure of interest. It has been used to measure venous oxygen saturation in the cerebral veins and detect hemorrhages or micro-bleeds [103]. A study reported that the measured venous oxygen saturation values in the second-trimester groups were higher than in the third-trimester group. This finding supports previous studies where blood oxygenation level (both pO2 and SO2) in umbilical venous blood samples was found to decrease with advancing gestational age. In addition, it is known that the cerebral blood flow rate to the human fetal brain increases from the second trimester to the third trimester. Altogether, the flow and oxygen saturation changes may occur to accommodate the increased metabolic demand usually seen during the third trimester. While QSM holds tremendous potential to measure the blood venous oxygen saturation non-invasively, more studies are needed to evaluate the feasibility of performing QSM in the human fetus. The following limitations have been outlined by the research group: (1) the mask generation using manual intervention was time-consuming; (2) a longer TE was used to achieve a good phase signal-to-noise ratio (SNR) in SWI. A shorter TE can prove to be more useful in QSM processing due to less T2* signal loss and phase aliasing inside and at the boundaries of the veins. Additionally, it could also help reduce the imaging time without sacrificing the phase SNR [103].

At seven days after birth, brain MRI is the standard of care for all infants at risk of hypoxic-ischemic cerebral injuries in full-term newborns undergoing hypothermia therapy [105, 106]. MRI of the brain in newborns is indicated for early evaluation of infarction, hemorrhage, injuries of prematurity, myelination, white and gray matter differentiation [107–109] (Fig. 11). Thayyil et al. included thirty-two studies (860 infants with NE) in the meta-analysis and compared conventional MRI vs. proton MR spectroscopy performed during the neonatal period with neurodevelopmental outcome at ≥one year [110]. Conventional MRI during the neonatal period (days 1–30) showed a pooled sensitivity of 91% (95% confidence interval [CI]: 87%–94%) and specificity of 51% (95% CI: 45%–58%). Late MRI (days 8–30) had higher sensitivity but lower specificity than early MRI (days 1–7). Proton MR spectroscopy allows identification of cerebral lactate, which persists for weeks following a significant hypoxic-ischemic injury. Proton MR spectroscopy deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio (days 1–30) had 82% overall pooled sensitivity (95% CI: 74%–89%) and 95% specificity (95% CI: 88%–99%). On common study analysis, Lac/NAA had better diagnostic accuracy than conventional MRI performed at any time during neonatal period.

Despite numerous advantages, there are material, technical and interpretative challenges, including elevated costs, limited accessibility, and limited time to acquire fast sequences, and limited training opportunities and expertise in the field of fetal MRI. In addition, MRI is more expensive to perform than in the US, with less equipment availability. Furthermore, it is impractical as an early screening tool or as a tool to optimize the therapy of HIE due to its non-portability and high cost.

IV. Nuclear medicine (PET, SPECT)

Nuclear medicine offers non-invasive imaging methods using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to study cerebral perfusion and metabolism [111]. The PET technique measures radiopharmaceuticals labeled with positron emitters using a PET scanner [112]. The unstable nucleus of radio-ligand emits positrons, combining with neighboring electrons to produce gamma-rays in the opposite direction at 180 degrees. These gamma rays are detected by the ring of detectors placed within the donut-shaped body of the scanner. The energy and location of these gamma rays are recorded and used by a computer program to reconstruct three-dimensional (3D) images of tracer concentration within the body.

Glucose metabolism provides the major energy supply required for brain function. Therefore, it is highly correlated with neuronal activity. In the newborn, the highest glucose metabolism was observed in the primary sensorimotor cortex, thalamus, brain stem, cingulate cortex, cerebellar vermis, and hippocampal region [113]. A study evaluating the correlation between glucose metabolism rate and gestational age was conducted on 36 preterm and term infants without brain injury and 24 infants with HIE. Cerebral glucose metabolic rate was increased with gestational age, especially at ≥ 37 weeks, and 18F-fluorodeoxyglucose uptake was lower in infants with HIE than in healthy term infants, especially in the subcortical white matter, thalamus, and basal ganglia areas, and correlated with the degree of severity of HIE, except for the basal ganglia [114]. In addition, a high correlation between cerebral glucose metabolism and the severity of HIE was detected in a study conducted on 20 term infants with HIE after perinatal asphyxia [115] (Fig. 12).

Quantitative measurement of cerebral blood flow can be obtained using injected H2O or inhaled CO_2 labeled with the isotope oxygen 15 [116]. In 1983, Volpe et al. [117], for the first time, demonstrated PET for determining regional CBF in neonates with major intraventricular hemorrhage and hemorrhagic intracerebral involvement. Later, the same group of investigators studied regional CBF by PET in 17 asphyxiated term infants during the acute period of illness. A study showed a relative decrease in CBF to parasagittal regions, generally symmetrical and more marked posteriorly than anteriorly. In addition, the single patient studied at postmortem examination exhibited parasagittal ischemic cerebral injury that correlated well with the PET abnormality of regional CBF [118].

SPECT is another type of nuclear medicine technique used to acquire the three-dimensional (3D) distribution of a radiopharmaceutical using a gamma camera [119]. Technetium-99m (Tc-99m) labeled compounds such as ethyl cysteine dimer (ECD), and hexamethyl propylene amine oxime (HMPAO) can be used to measure cerebral perfusion. These agents are unstable and are able to cross the blood-brain barrier in their lipophilic form and are retained within the brain by their conversion into hydrophilic form, which is unable to pass the blood-brain barrier and is trapped in the brain. Their extraction from plasma to the brain occurs rapidly within 1–2 minutes. This initial tracer uptake remains almost unchanged for several hours, allowing the acquisition of a constant image of regional cerebral blood flow at the time of tracer injection [120]. A prospective cohort study of CBF using SPECT was conducted in tertiary level ICU [121]. Shah et al. evaluated CBF on SPECT scan in neonates with HIE, CBF correlation with immediate neurological status and neurodevelopmental

outcome, as well as comparison of SPECT to ultrasonography. Results showed that the most common pattern of defect noted was parasagittal hypoperfusion. Neonates with severe perfusion defects had a higher incidence of difficulty to control seizures and longer duration of altered sensorium. The study concluded that SPECT scan is superior to ultrasonography in predicting neurodevelopmental outcomes in neonates with HIE.

Several limitations restrict the use of nuclear medicine in neonates. PET uses ionizing radiation, and the technique is not widely available (there is a need for proximity to a cyclotron) because the tracer has an extremely short half-life [122]. Moreover, PET is not available at the bedside or for emergencies. Another disadvantage of PET scanners is their operating cost [123]. SPECT is a suitable bedside method that is cheaper and more widely available than PET imaging. The greatest disadvantage of using the SPECT technique in children is the ionizing radiation. The technique also yields poor resolution and requires a long examination time (20–25 minutes). In addition, data processing to obtain maps takes about 5 minutes.

Emerging diagnostic technologies for monitoring fetal and neonatal brain status

I. Photoacoustic (PA) Imaging

In recent years, a novel US-based modality called photoacoustic (PA) imaging has shown tremendous potential by providing complementary functional and cellular, and molecular information [124–129]. The key advantage that makes PA imaging a suitable diagnostic modality for clinical applications is the ability to provide functional images (e.g., tissue vascularity and SO_2 level) at clinically relevant depths (> 30 mm, depending on tissue type) with high resolution (typically < 200 μm, depending on the acoustic resolution for deep-tissue imaging) and in real-time. Moreover, PA imaging can be easily combined with US imaging because both modalities use similar acquisition hardware components and signal detection regimens. Therefore, combining the US and PA imaging makes it possible to simultaneously obtain anatomic and functional information [124, 125, 130]. In PA imaging, short (typically in the nano-seconds range) laser pulses are utilized to excite the tissue chromophores such as oxy- and de-oxyhemoglobin, and consequent acoustic signals (PA signals) [124, 128] is acquired by an acoustic (or ultrasonic) receiver to form PA images that are representing the tissue's optical absorption map. In addition, similar to NIRS, the contrast between oxy- and deoxy hemoglobin provides PA with a unique capability to measure the blood oxygen saturation (SO_2= ratio of oxy- to total hemoglobin). PA imaging has been previously applied for breast cancer, melanoma, osteoarthritis imaging, cerebral blood oxygen saturation assessment, and neuro-vasculature evaluation with and without functional hemodynamics [131–134]. Like US imaging, a major challenge in PA imaging of the brain is that the skull limits the penetration depth and causes image distortions due to acoustic aberrations [135, 136]. However, fetuses and neonates are more suitable for PA imaging due to their relatively thin skull and open fontanelles [137–140]. These unique anatomical properties create minimal optical, ultrasonic attenuation and distortion as compared to adults.

The use of a single-element US transducer for non-invasive trans-fontanelle PA imaging of neonatal brains is reported in the literature (Fig. 13) [139, 141]. Two laser excitation wavelengths, 752 and 797 nm, were selected for spectroscopic PA (sPA) and are suggested to be suitable for spectral unmixing and differentiation between oxy- and deoxy-hemoglobin. The results revealed that the PA imaging could detect the blood SO_2 in a vessel through the infant skull at 5 mm depth (Fig. 13 a and b). sPA imaging results indicated a high correlation between the measurements to the gold standard pulse-oximeter (Fig. 13 c). Another group proposed an integrated US, US Doppler, and PA imaging system around a clinical transvaginal US probe [133] (Fig. 14). Their proposed multi-parametric imaging system aims to visualize blood flow and estimate the blood SO_2 in venous and arterial vessels, such as superior sagittal sinus (SSS) and cortical branches of the anterior cerebral artery (ACA). Estimating the SO_2 in selected vessels and combining it with quantitative arterial and venous blood flow (measured by fractional moving blood volume (FMBV)) allows the calculation for metabolic rate of oxygen consumption ($CMRO_2$) in the fetal brain. This proposed multi-parametric imaging probe have clinically acceptable size for an intrapartum imaging (total diameter 29 mm, Fig 14. a–c), high accuracy in monitoring blood volume (Fig 14. d), and blood oxygenation level (Fig 14. e). Therefore, it may pave the way for developing effective diagnostic modalities and favorable fetal and maternal outcomes.

In summary, the integrated US and PA imaging technology have the following advantages in imaging fetal and neonatal brains. First, the PA signal directly measures cerebral venous oxygenation with high spatial resolution, accurate blood oxygenation measurements, and continuous real-time monitoring. Second, the SO_2 levels in the ACA and SSS estimated by sPA in combination with blood flow detected by US Doppler give the accessibility for calculating $CMRO_2$, which may help to potentially lower the risk of hypoxic events during delivery and labor. Additionally, summarizes the performance of existing clinical diagnostic tools and emerging technologies in detecting HIE and NE.

Conclusion

HIE is a significant cause of morbidity and mortality in the neonatal period, and cerebral palsy is a late neurologic sequela in the postnatal period. The Cranial Ultrasound (CUS) provides a convenient, non-invasive, relatively low-cost screening examination of the hemodynamically unstable neonate at the bedside. CT has the least sensitive modality for the evaluation of HIE for poor parenchymal contrast resolution. The most sensitive and specific imaging technique for examining infants with suspected HIE is MR imaging. CUS, CT, MRI, nuclear medicine techniques, each with its advantages and disadvantages, show characteristic patterns of brain injury that correlate well with the degree of hypotension and the level of brain maturity at the time of the insult, thus excluding other causes of encephalopathy. The development of an ideal fetal and neonatal neuroimaging modality is an ongoing challenge within the world of intrapartum care and neonatal intensive care medicine. Innovations including low radiation, rapid CT, and diffusion-weighted MRI have changed the approach to which infants with neurologic dysfunction are evaluated and managed. However, despite these advances, we continue to lack the ability to non-invasively detect and follow structural and functional variations in real-time at the bedside of a critically ill neonate. In recent years, a novel ongoing imaging modality, photoacoustic

(PA) imaging, has shown the potential to develop a point-of-care, non-invasive, real-time method to monitor cerebral hemodynamic, assess the cortical injury and assist in developing neuroprotective strategies within the walls of the neonatal intensive care and intrapartum units. It may pave the way for developing practical solutions and good fetal and neonatal care and potentially lower the risk of hypoxic events in fetuses and newborns.

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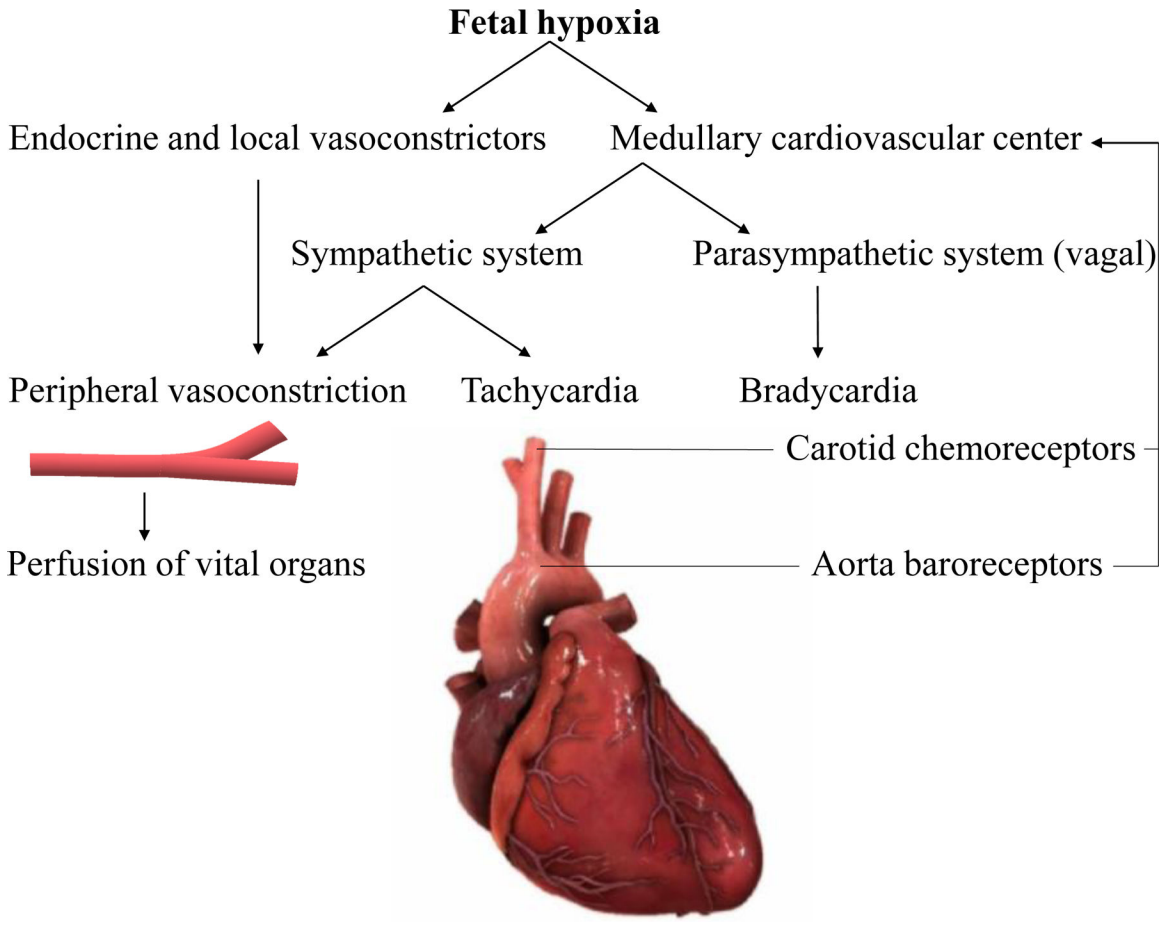

Fig. 1.

Physiology of fetal brain sparing during hypoxia. Carotid chemoreflex activation leads to bradycardia through the vagal nerve stimulation and increase in peripheral vasoconstriction. Hormones and local vascular mediators further maintain peripheral vasoconstriction.

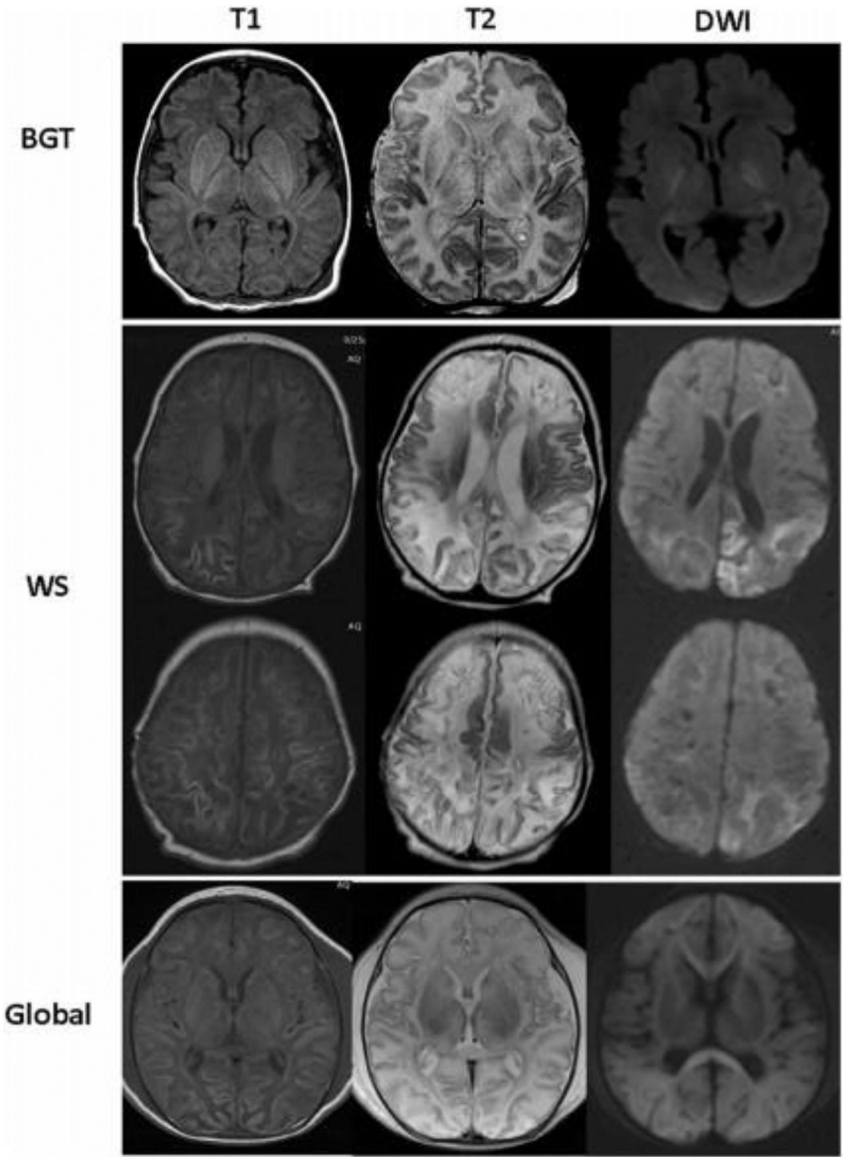

Fig. 2.

Patterns of brain injury in neonates with HIE on T1-weighted, and diffusion-weighted (DWI) images. BGT, basal ganglia/thalamic predominant injury; WS, watershed injury with cortical laminar necrosis and subcortical white matter injury, and global pattern with total cerebral injury (Adopted from [11] Figure 1)

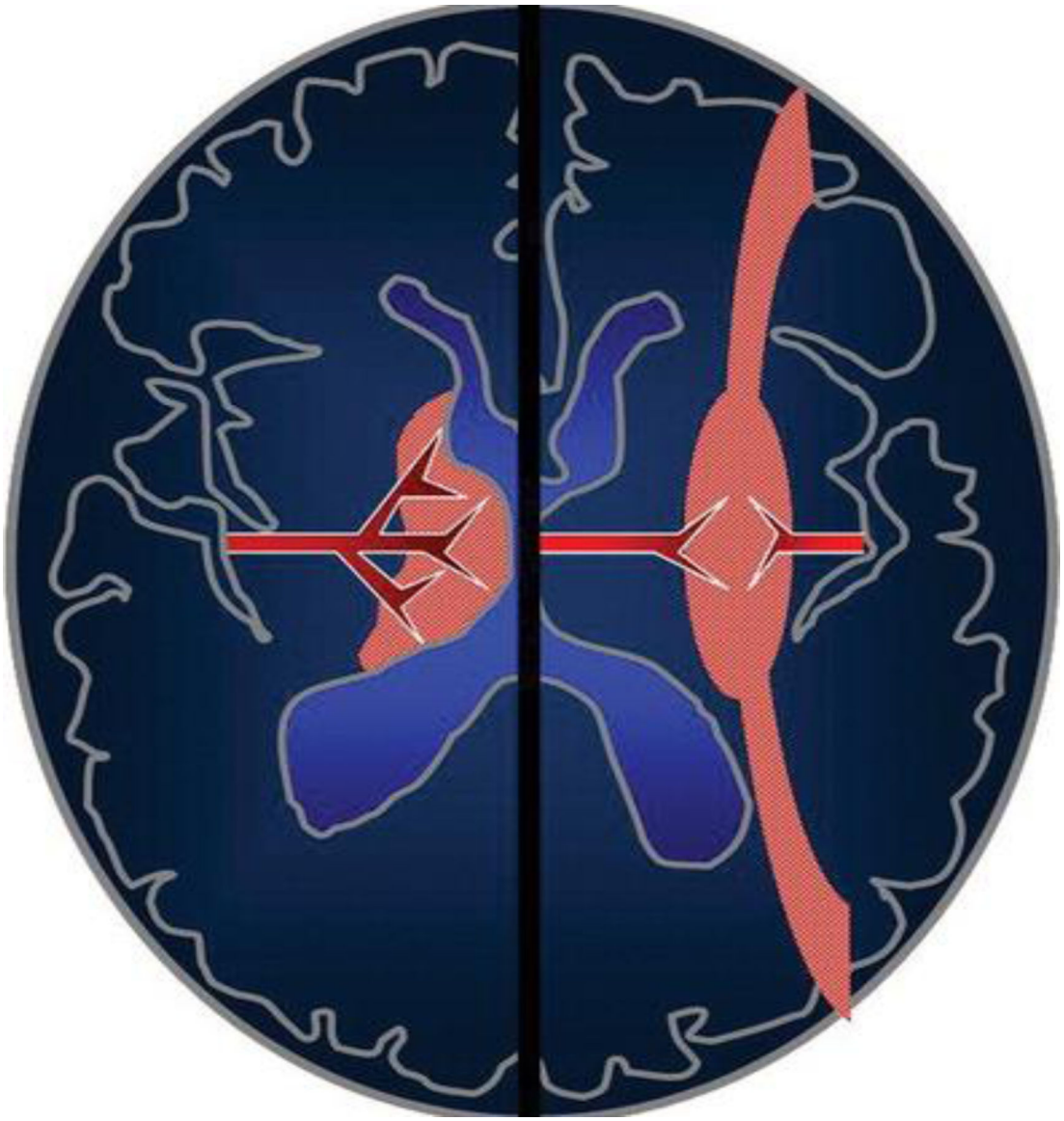

Fig. 3.

Patterns of brain injury in HIE. Schematic shows the premature neonatal brain (left side) and term infant brain (right side). It illustrates how the vascular supply changes with maturation and affects the pattern of brain injury in HIE. The premature neonatal brain (left side) has a ventriculopetal vascular pattern, and hypoperfusion results in a periventricular border zone (red shaded area) of white matter injury. In the term infant (right side), a ventriculofugal vascular pattern develops as the brain matures, and the border zone during hypoperfusion is more peripheral (red shaded area) with subcortical white matter and parasagittal cortical injury. (Adopted from [24] Figure 2)

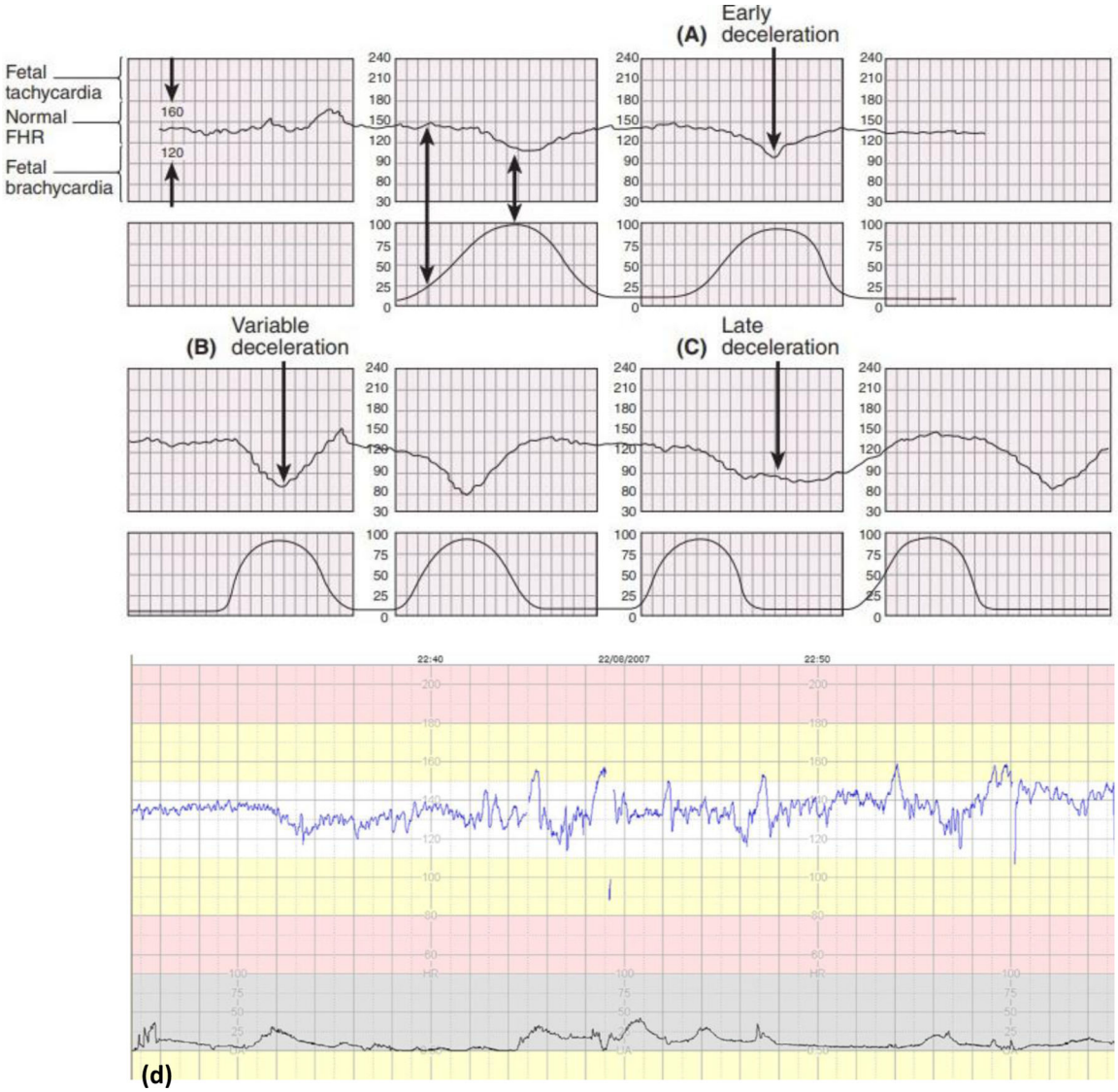

Fig. 4.

Fetal Heart Rate patterns (a) Early deceleration. (b) Variable deceleration. These decelerations may start before, during, or after a uterine contraction starts. (c) Late deceleration. The onset, nadir, and recovery of the deceleration occur, respectively, after the beginning, peak, and end of the contraction (Adopted from [45] Fig. 9.11). (d) An example of normal CTG showing stable baseline fetal HR of about 130 bpm. It shows no decelerations, normal baseline variability, accelerations, and fetal cycling activity (Adopted from [47]).

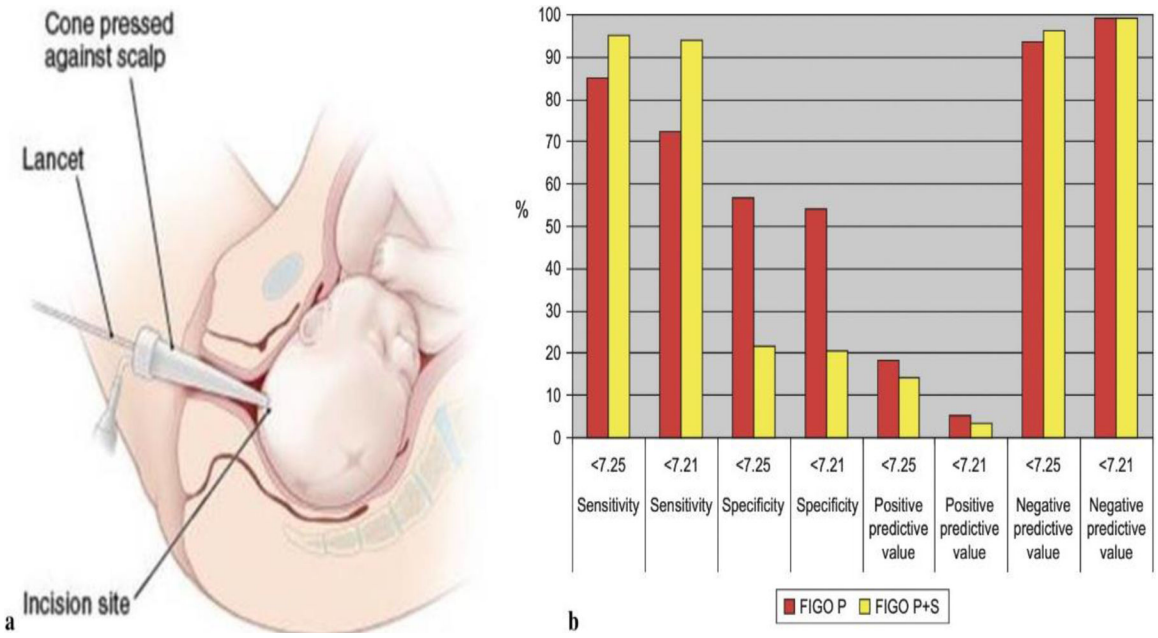

Fig. 5.

(a) Fetal scalp Blood Sampling. The Figure shows the incision site of the lancet and placement of the cone against the scalp. (Adopted from [45] Fig 9.12). (b) Shown the sensitivity and specificity for fetal scalp PH values as well as active and negative predictive values for pathological (P), and pathological and suspect (P + S) FIGO criteria. (Adopted from [14]).

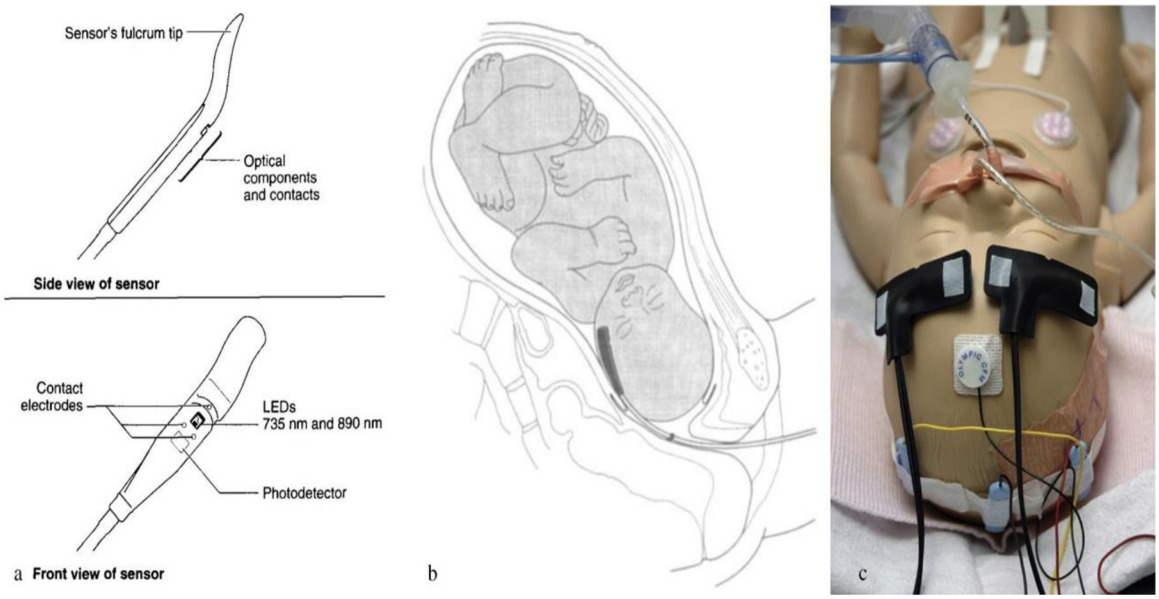

Fig. 6.

The FSpO2 monitoring system: a) and b) show a single use, sterile, disposable sensor that is inserted through the cervix into the uterus which rests against the fetal temple, cheek or forehead (Adopted from [70] Figure 1 and 2), c) shows position of the NIRS sensors for the purpose of monitoring continuously mixed venous saturation, two neonatal NIRS sensors are placed respectively on each side of the newborn' s forehead, over the area of frontal lobes. (Adopted from [69] Figure 1).

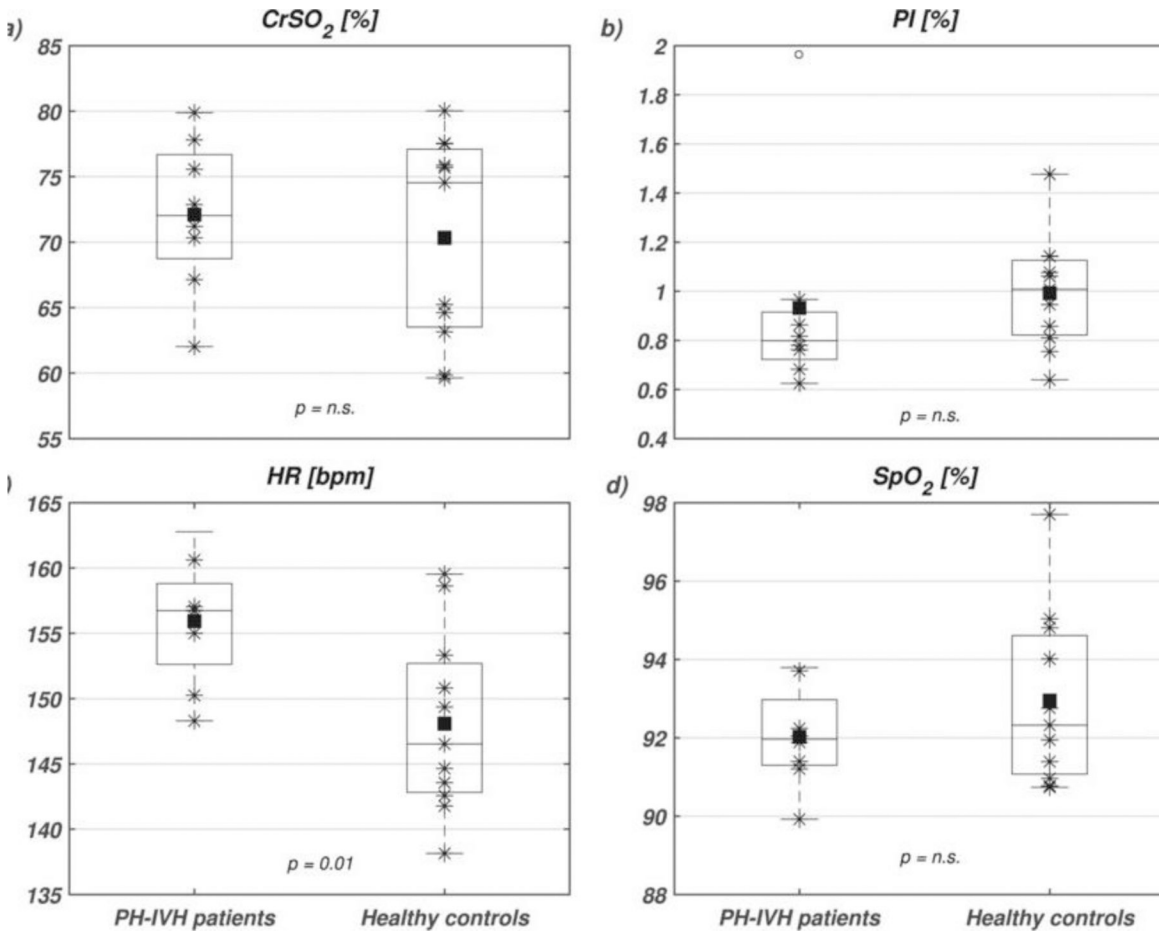

Fig. 7.

Boxplots of (a) near infrared spectroscopy (NIRS) cerebral regional haemoglobin oxygen saturation (CrSO2), (b) peripheral perfusion index (PI), (c) heart rate (HR) and (d) capillary oxygen saturation (SpO2) in PH-IVH patients (left boxplots) and healthy age-matched controls (right boxplots). On each box, the central mark is the median, the square is the mean, the stars are the individual data, the edges of the box are the 25th and 75th percentiles, and the whiskers show the 95%onfidence interval. Empty circles denote outliers and statistical comparisons are indicated with corresponding p-values (n.s., non-significant). (Adopted from [71] Figure 1).

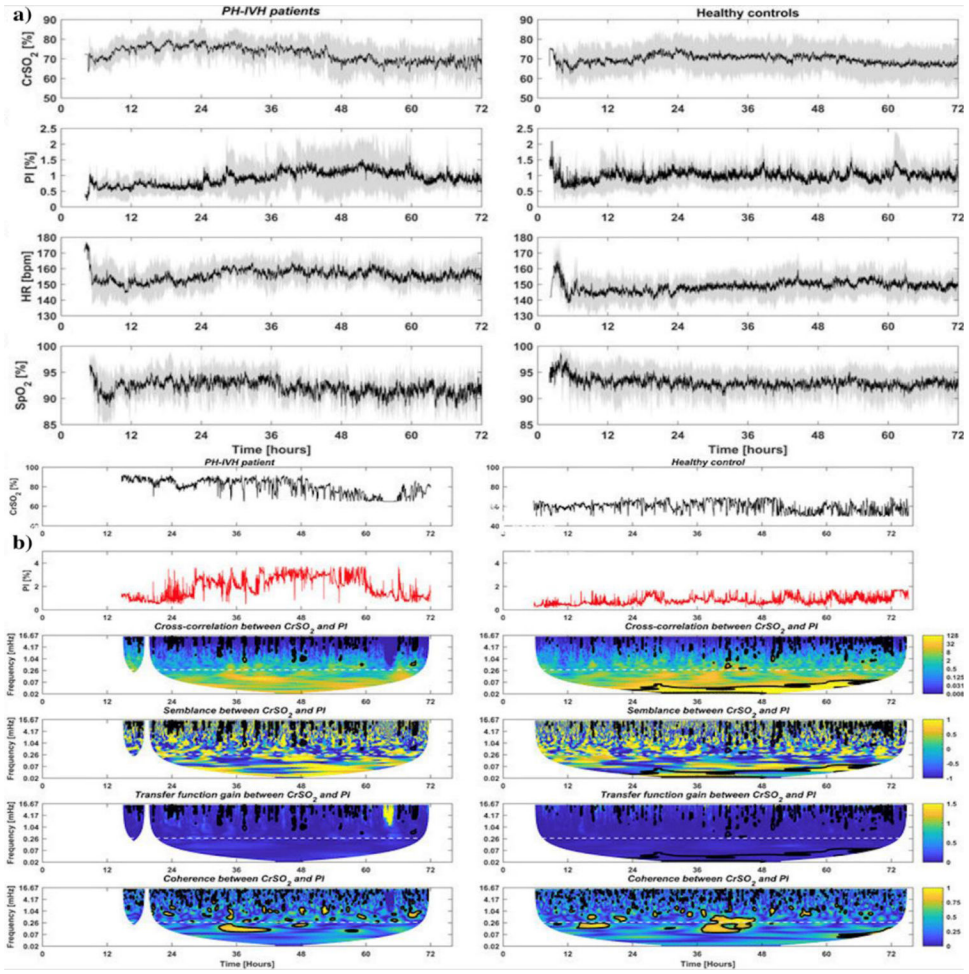

Fig. 8.

(a) Temporal distributions of (first line) near infrared spectroscopy (NIRS) cerebral regional hemoglobin oxygen saturation ($CrSO_2$), (second line) peripheral perfusion index (PI), (third line) heart rate (HR) and (fourth line) capillary oxygen saturation (SpO_2) in PH-IVH patients (left column) and healthy age-matched controls (right column) in the first 72 hr of life. On each plot, the black curve is the mean, and the grey shaded region represents one standard deviation of the group. (b) Example of the complete analytical workow in a healthy control (left column) and in an infant with pulmonary (PH) and/or intraventricular haemorrhage (IVH, right column): (first line) and (second line) depict temporal distributions of near infrared spectroscopy (NIRS) cerebral regional hemoglobin oxygen saturation ($CrSO_2$) and peripheral perfusion index (PI) in the first 72 hr of life, respectively; (third-sixth line) display the amplitude of the cross-correlation, the semblance (anti-phase and in-phase), the amplitude of the gain (transfer function) and the coherence between $CrSO_2$ and PI in the time-frequency space. Regions that are statistically significant are comprised in a black bold contour. A dashed white line indicates the selected ultra-frequency band of slow and prolonged periods of >1 h (<0.28 mHz) used for statistical analysis. (Adopted from [71] Figure 2 and 3).

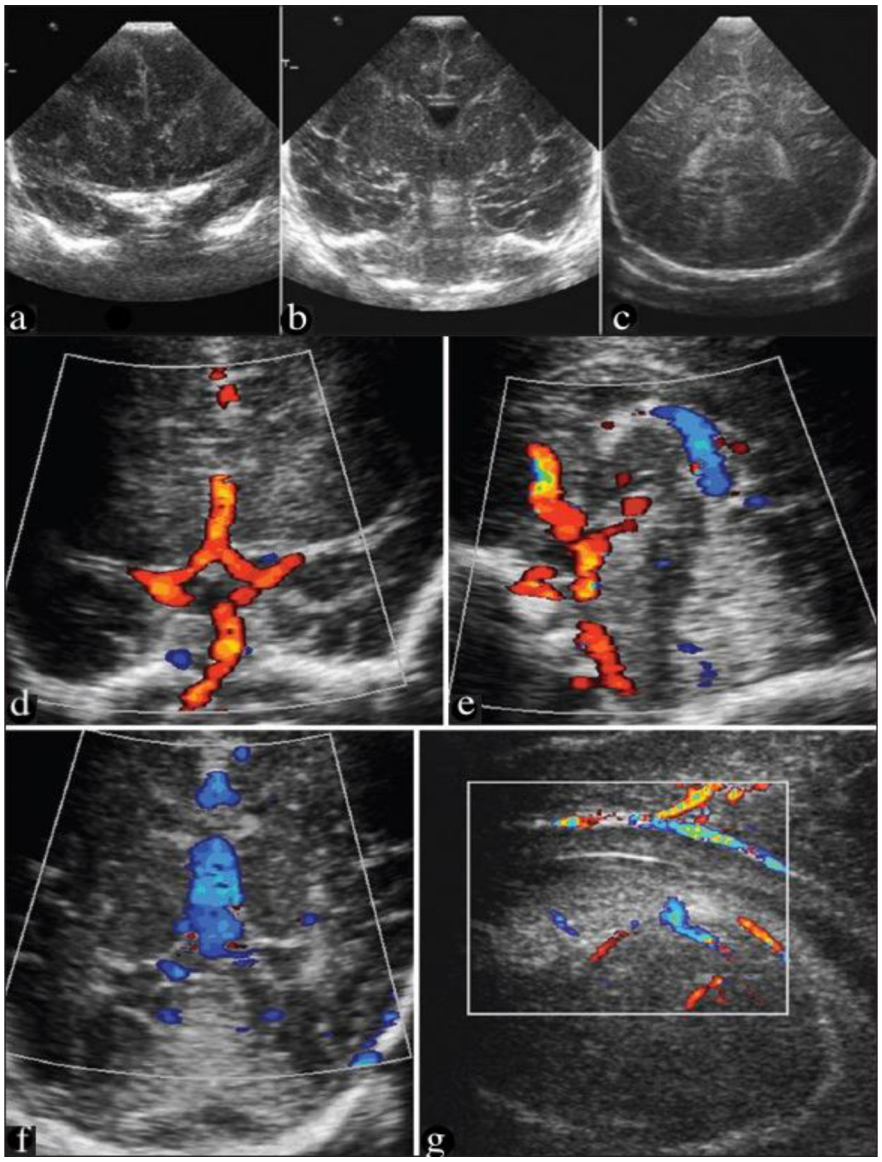

Fig. 9.

Coronal USG at the level of frontal lobes (a), foramina of Monro (b), and trigone (c), demonstrating the interhemispheric fissure, lateral ventricles, and periventricular parenchyma. Doppler images (d & e) demonstrating the circle of Willis. Coronal USG is demonstrating the vein of Galen, f) a parasagittal study showing the small periventricular veins in the region of the caudothalamic groove (g). (Adopted from [80] Figure 9 A-D and Figure 6 A-C).

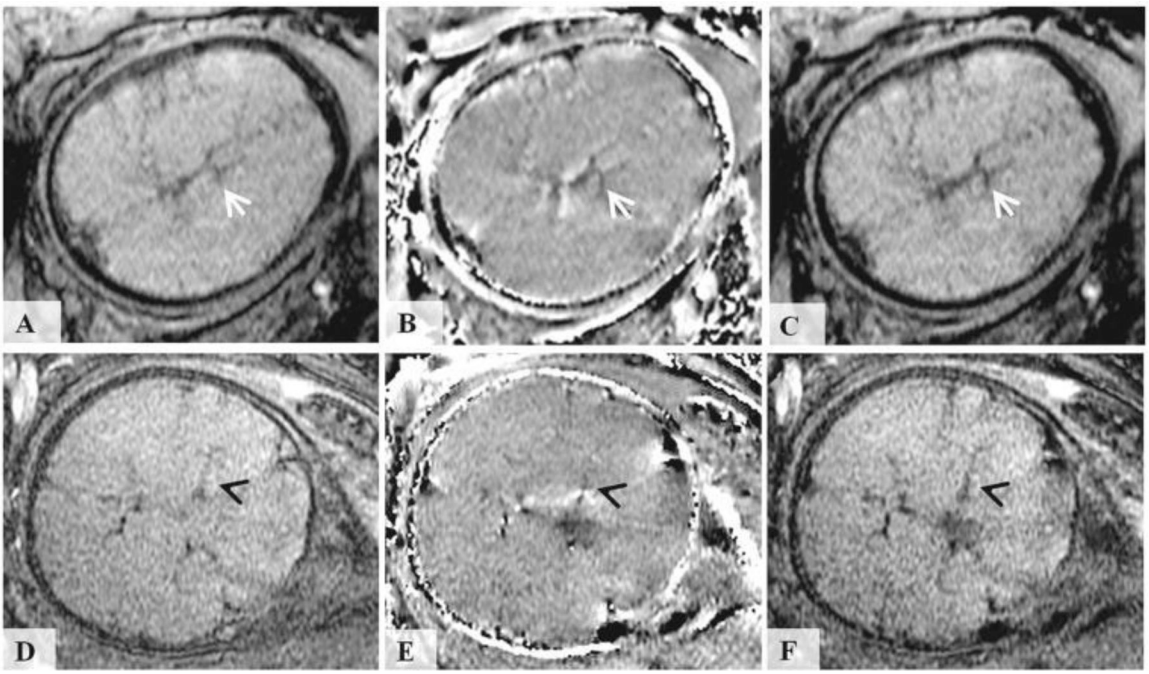

Fig. 10.

Susceptibility weighted images of the fetal brain. The top row images were acquired in the axial orientation relative to the fetus using 3D SWI sequence at 3.0T field strength from a fetus at 36 weeks of gestation. The bottom row images were acquired in coronal orientation relative to the fetus using a 2D SWI sequence at 1.5T field strength from a fetus at 35 weeks of gestation. Fig (a, d) show the original magnitude images. Fig (b, e) corresponds to filtered phase images. Fig (c, f) corresponds to susceptibility weighted magnitude image (SWI). (Adopted from [97] Figure 1).

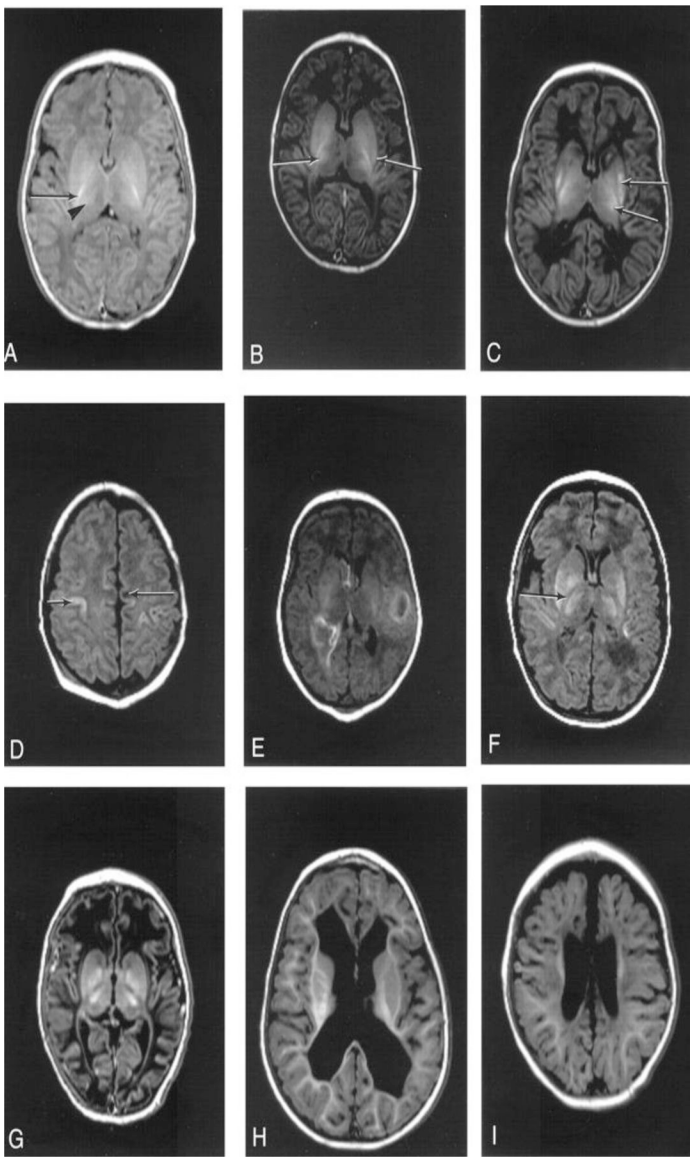

Fig. 11.

Patterns of injury identified on neonatal MRI. A, Normal appearances control term infant 2 days old). There are: normal high signal from myelin in the posterior half of the PLIC (arrow), more diffuse high signal in the lateral thalamus secondary to myelination in the nuclei (arrowhead), normal gray/white matter differentiation in the cerebral hemispheres. B, Mild basal ganglia: infant 4 days old with stage 2 HIE. There are small focal high-signal areas in the inferior thalamus and lentiform. C, Moderate basal ganglia: infant 20 days old with stage 2 HIE. There are: focal high-signal intensity regions in the lentiform and thalami (arrows), equivocal signal intensity within the PLIC (arrowhead). D, Moderate white matter: infant 20 days old with stage 2 HIE. There are: areas of focal low-signal intensity in the subcortical white matter (arrow), abnormal high-signal intensity in the cortex around the central sulcus (arrowhead). E, Severe white matter with hemorrhage: infant 5 days old with stage 2 HIE. There are: areas of high-signal intensity consistent with hemorrhage and areas

of loss of gray/white matter differentiation. F, Severe basal ganglia lesions: infant 8 days old with stage 2 HIE. There are: abnormal areas of high-signal intensity in the lentiform and thalami, abnormal low-signal intensity within the PLIC. G, Severe basal ganglia, and severe white matter lesions: infant 11 days old with stage 2 HIE. There are: abnormal signal intensity in the basal ganglia and thalami, loss of the normal high-signal intensity from myelin within the posterior limb, abnormal low-signal intensity in the white matter with loss of the normal gray/white matter differentiation, particularly in the frontal lobes. H, Follow-up imaging/ventricular dilatation: infant 1 year 5 months of age with stage 2 HIE (same case as E). There is marked irregular dilatation of the ventricles. The extracerebral space is normal. I, Follow-up imaging/ventricular dilatation with widened extracerebral space: infant 1 year old with stage 2 HIE (same case as G). There is moderate ventricular dilatation and widening of the frontal extracerebral space and interhemispheric fissure. (Adopted from [109] Figure 1.)

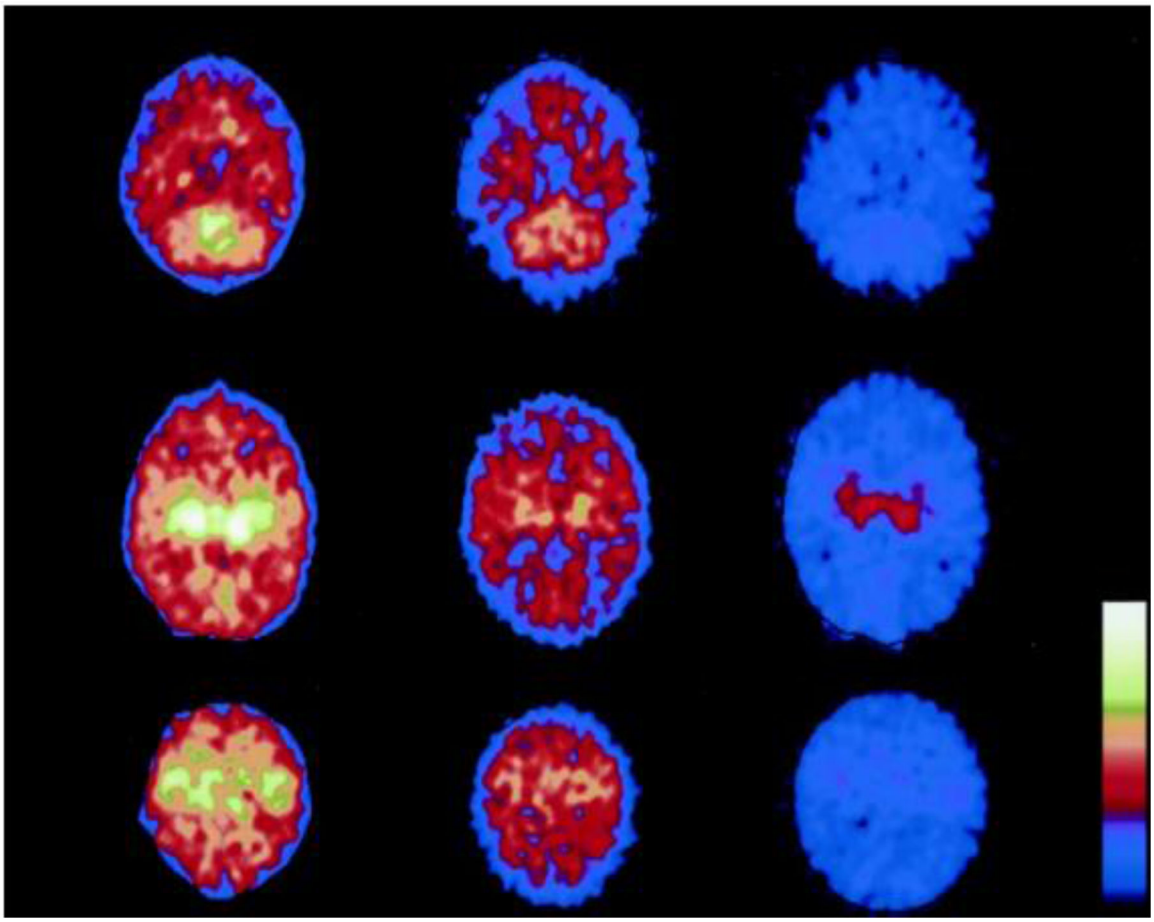

Fig. 12.

Total and regional cerebral glucose metabolism (CMRgl) measured in the subacute period (10–11 d) after birth asphyxia in three infants with different degrees of HIE. PET scan shows that the most metabolically active brain areas were the deep subcortical parts, thalamus, basal ganglia, and sensorimotor cortex, whereas the cortical areas (frontal, parietal, and occipital regions) were less metabolically active. Regional CMRglc in cerebellum (top), thalamus (middle), and sensorimotor cortex (bottom). The infant to the right (HIE-3) has developed CP (tetraplegia) with complicated seizures. The infant to the left (HIE-1) is healthy (2-y follow-up). The scale of the different images is identical. (Adopted from [115] Figure 2.)

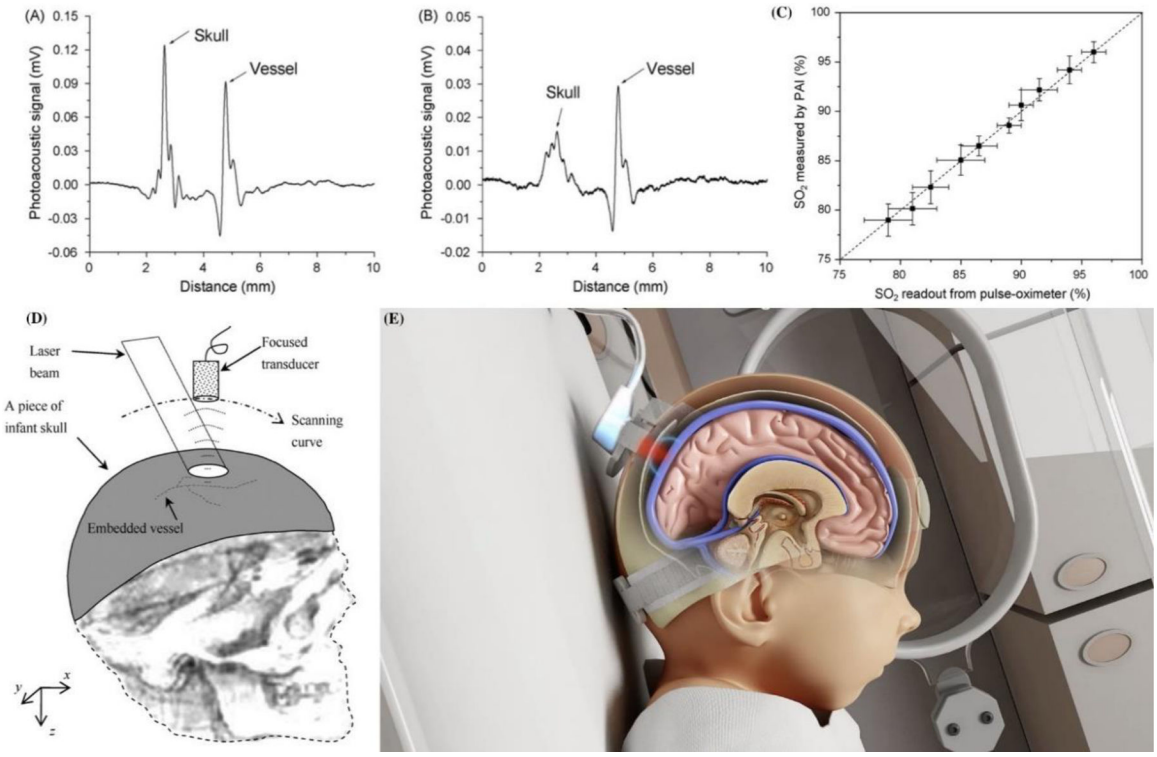

Fig. 13.

Single element focused USPA system for imaging the neonatal brain. Fig (A) & (B) show photoacoustic signals from a vessel embedded beneath the infant skull, where (A) is induced by solid-beam illumination and (B) is induced by dark-field illumination. Fig (C) shows photoacoustic measurements of the blood oxygenation levels through the infant skull in comparison with the readouts from a pulse-oximeter. Fig (D) represents the geometry of reflection mode transcranial photoacoustic imaging of brain. Adopted from [139]). Fig (E) Noninvasix® Photoacoustic oxymetry System. Noninvasix's system utilizes optoacoustic monitoring of cerebral venous oxygenation to accurately measure the amount of oxygen a neonate is receiving in real time.

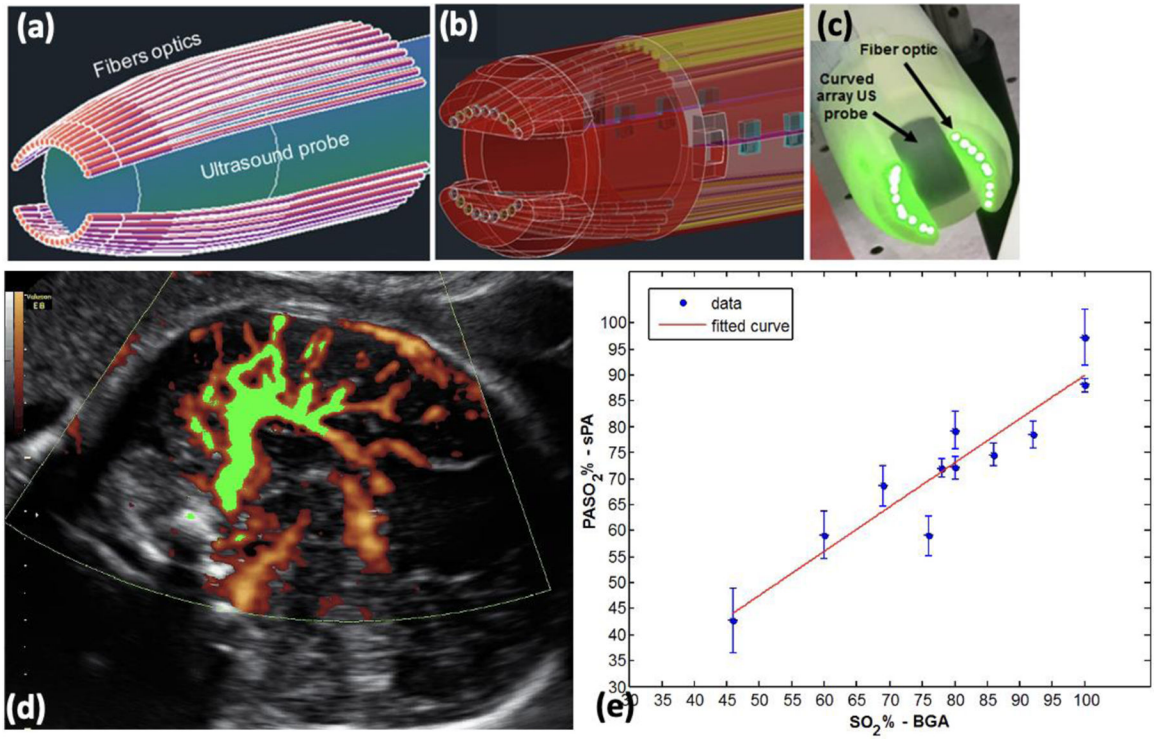

Fig. 14.

(a) Schematic of a TVUS and fiber optics light delivery. (b) CAD design of fiber holding sheath. (c) Photograph of the prototype an Endocavity US and PA probe, which illuminates the target tissue with a focused (line-like) illumination pattern at 25 mm away from probe surface. The system has a diameter of 29 mm (under clinical requirements for transvaginal imaging). It can provide functional and molecular images at high resolution (200 μm @ 25 mm depth), and high penetration depth (> 20 mm) in brain. (d) Normalized FMBV image (green mask) overlaid on top of acquired Doppler image, indicating the blood volume is 31%. (e) Blood SO_2 measure by sPA vs. gold standard blood gas analysis. A high correlation (R^2=0.87) was found between sPA measurements of blood SO_2 and the gold standard. These results suggest high accuracy and reliability of sPA imaging to evaluate blood oxygenation. The 46% oxygenation, as the lowest SO_2 level is relatively close to the fetal SO_2 threshold during labor (%35 to %40). (Adopted from [133]).

Table 1.

Performance of existing clinical diagnostic tools and emerging technologies in detecting HIE and NE.

Method [References]	Advantages	Limitations
External fetal heart rate monitoring (FHRM) References: [25–29, 45–49, 142–146]	• Non-invasive method providing continuous tracing of FHR • Allows monitoring frequency and duration of uterine contractions • Low cost	• Poor sensitivity, leading to an increase in operative deliveries • Maternal movement dependency • Low specificity for prediction of the cerebral palsy, high false-positive rate as high as 99.8%
Internal fetal heart rate monitoring (FHRM) References: [25–29, 45–49, 142–146]	• Accurate and consistent transmission of fetal HR, not affected by maternal movements • Low cost	• Invasive modality, causing an increased risk of infection and bruising of the fetal scalp or other body parts • Some conditions preclude fetal scalp electrode application (maternal HIV infection, active herpes simplex virus infection, hepatitis B and C, and coagulation disorders)
Fetal scalp blood sampling (FBS) References: [14, 51–54, 147]	• Allows for direct assessment of the acid base balance of the fetus and neonate • Reduces the increase in cesarean deliveries associated with the use of continuous FHR monitoring	• Invasive and can be uncomfortable for the laboring woman • Discontinuous nature • Causes an increased risk of infection and hemorrhage • Requires membranes to be ruptured, and 2–3 cm dilated cervix • Multiple sampling is impractical and can result in fetal blood loss
Cranial ultrasound (CUS) References: [22, 80–85]	• Safe, non-invasive, and does not use ionizing radiation • Portability and low cost • Evolution of lesions can be monitored	• Operator dependency • Small field of view • Limited soft-tissue acoustic contrast, beam attenuation by adipose tissue, poor image quality in oligohydramnios
Magnetic resonance imaging (MRI) References: [89–93, 97, 98, 100, 103–110]	• High sensitivity • Good soft tissue contrast and characterization and access to functional data, e.g., diffusion-weighted imaging (DWI) • Allows for perfusion-weighted imaging (PWI), blood oxygenation dependent (BOLD) contrast, MR spectroscopy (MRS) and larger field of view (FOV)	• Non-portability and high cost • Requires sedation • Time-consuming
Computed tomography (CT) References: [60–67]	• Rapid image acquisition with minimal use of sedation	• Radiation exposure • Low sensitivity
Nuclear imaging (PET, SPECT) References: [111–123]	• Non-invasive	• Radiation exposure • High operating cost • Not available at the bedside or for emergencies • Requires sedation

Method [References]	Advantages	Limitations
		• Time-consuming
Near-infrared spectroscopy (NIRS) References: [68, 69, 71–79]	• Non-invasive • Available at the bedside without interrupting routine care • Allows for continuous monitoring of cerebral oxygenation	• Monitoring depends on vessel variation, - given that the percentage of arteries, capillaries, and veins mixing in the brain circulation is not constant • Measurements are affected by hemoglobin variations. Hemodilution, transfusion, hypocapnia and hypercapnia lead to significant variations in cerebral oximetry
Photoacoustic (PA) imaging References: [124–140]	• Non-invasive, non-ionizing, fast, inexpensive, and portable • High sensitivity for imaging cerebral vasculature • Allows for continuous real-time monitoring • Direct measurement of cerebral venous oxygenation with high spatial resolution	• Novel modality, requiring further approval