The physiology of intrapartum fetal compromise at term

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In the majority of women, placental function is sufficient to allow appropriate growth of the fetus throughout pregnancy and to help shield it from the hypoxic stresses of labor. In some women, depending on the degree of placental dysfunction, fetal growth restriction may ensue or intrapartum fetal compromise may develop if the placenta is not able to meet the extra fetal demands required during the last few weeks of pregnancy or during labor and thereby predispose these infants to hypoxic insults. If severe enough, these can result in emergency operative birth, death, short-term morbidity, and significant long-term neurodevelopmental issues.

Globally, perinatal hypoxia remains a major contributor to stillbirth, hypoxic ischemic encephalopathy (HIE), and cerebral palsy; 10% of the global burden of disease is attributable to newborn conditions. It is estimated that worldwide, 23% of the 4 million neonatal deaths per year occur because of intrapartum complications.[1,2] Of newborns who develop HIE, almost 1 million die in the first month of life and 25% of survivors have long-term sequelae such as

Uterine contractions in labor result in a 60% reduction in uteroplacental perfusion, causing transient fetal and placental hypoxia. A healthy term fetus with a normally developed placenta is able to accommodate this transient hypoxia by activation of the peripheral chemoreflex, resulting in a reduction in oxygen consumption and a centralization of oxygenated blood to critical organs, namely the heart, brain, and adrenals. Providing there is adequate time for placental and fetal reperfusion between contractions, these fetuses will be able to withstand prolonged periods of intermittent hypoxia and avoid severe hypoxic injury. However, there exists a cohort of fetuses in whom abnormal placental development in the first half of pregnancy results in failure of endovascular invasion of the spiral arteries by the cytotrophoblastic cells and inadequate placental angiogenesis. This produces a high-resistance, low-flow circulation predisposing to hypoperfusion, hypoxia, reperfusion injury, and oxidative stress within the placenta. Furthermore, this renders the placenta susceptible to fluctuations and reduction in uteroplacental perfusion in response to external compression and stimuli (as occurs in labor), further reducing fetal capillary perfusion, placing the fetus at risk of inadequate gas/nutrient exchange. This placental dysfunction predisposes the fetus to intrapartum fetal compromise. In the absence of a rare catastrophic event, intrapartum fetal compromise occurs as a gradual process when there is an inability of the fetal heart to respond to the peripheral chemoreflex to maintain cardiac output. This may arise as a consequence of placental dysfunction reducing pre-labor myocardial glycogen stores necessary for anaerobic metabolism or due to an inadequate placental perfusion between contractions to restore fetal oxygen and nutrient exchange. If the hypoxic insult is severe enough and long enough, profound multiorgan injury and even death may occur. This review provides a detailed synopsis of the events that can result in placental dysfunction, how this may predispose to intrapartum fetal hypoxia, and what protective mechanisms are in place to avoid hypoxic injury.

Key words: fetal hypoxia, hypoxic ischemic encephalopathy, inadequate placentation, intrapartum fetal compromise, peripheral chemoreflex, physiology, placental development

cerebral palsy with intrapartum hypoxia, accounting for 1 in 5 cases in term infants.[3] Indeed, the World Health Organization estimates that disability-adjusted life years due to neonatal encephalopathy, birth asphyxia, and birth trauma are comparable with congenital malformations, type II diabetes, and HIV/AIDS (54,400 million).[4]

Although rare, unpredictable and acute catastrophic events such as placental abruption, uterine rupture, or cord prolapse are associated with a high risk of severe fetal hypoxia; 75% of cases in labor occur gradually as a result of

uterine contractions.[5] Uterine contractions reduce uteroplacental perfusion by as much as 60%[6] and although most fetuses are able to tolerate this reduction in placental perfusion, there exists a cohort that are unable to and are at risk of hypoxic injury. Fetuses that are unable to withstand these periods of intermittent hypoxia manifest their compromise in a variety of ways, including heart rate abnormalities (decelerations, decrease in beat-to-beat variability etc) and passage of meconium in utero. In extreme cases, if the hypoxic insult is severe enough, brain injury or death can ensue. This

review will cover the physiology of placental development, fetal response to intrapartum hypoxia at term, and some recent advances in the screening and identification of vulnerable fetuses.

Placental Development

Development of the placenta involves 2 complex but concurrent processes: endothelial invasion of the maternal spiral arteries by cytotrophoblast (CT) cells and development of the fetal vascular tree. Endothelial invasion initially results in the formation of a trophoblast "plug," which results in a relatively hypoxic milieu (oxygen partial pressure [PaO_2] <20 mm Hg) within the intervillous space.[7,8] This hypoxic environment is crucial for early regulation of CT proliferation and differentiation.[9] The CT plug dissipates after 10 weeks of gestation, resulting in increased placental blood flow and PaO_2.[10] Endovascular invasion by the CTs into the wall of the spiral arteries involves de-differentiation of adhesion molecules and conversion from an epithelial to endothelial phenotype.[11] By the late second trimester, the inner third of the myometrial spiral arteries are exclusively lined by CT endothelial cells,[12] replacing the normal vascular smooth muscle with a noncontractile matrix that is nonresponsive to neuronal and hormonal stimuli.[13,14] These remodeled vessels dilate 4-fold at their terminal portion,[15] into low-resistance, high-capacitance channels capable of increasing the supply of oxygen and nutrients to the fetus to meet its growing demands through gestation.[16] This process is mediated by the interplay of several paracrine factors, including vascular endothelial growth factor, soluble fms-like tyrosine kinase-1,[17,18] and insulin-like growth factor peptides I and II,[19,20] which are in turn modulated by pregnancy-associated plasma protein (PAPP-A) produced by trophoblast cells.[21] Low PAPP-A levels are associated with decreased bioavailability of insulin-like growth factor peptides, limiting trophoblastic invasion[22] and a range of pregnancy disorders associated with abnormal placentation.[23−26]

Concurrent to trophoblast invasion is the development of new vessels within the placenta. This occurs through the processes of vasculogenesis (differentiation of mesenchymal-derived hemangioblasts into endothelial cells)[27] and angiogenesis (remodeling and expansion of existing vessels either by branching or non-branching processes), which are modulated by vascular endothelial growth factor in first half of pregnancy[28,29] and placental growth factor (PlGF) after 23 weeks gestation.[30,31]

Failure of endovascular invasion of the spiral arteries produces a high-resistance, low-flow circulation that predisposes to hypoperfusion, hypoxia, reperfusion injury, and oxidative stress in the placenta.[32] This affects placental function through several mechanisms— the persistent high-pressure flow through the intervillous space (2-3 m/s compared with 10 cm/s in normally dilated vessels) results in increased sheer stress and damage to the syncytiotrophoblasts lining the chorionic villi, thereby compromising the functional capacity of the villi for gas and nutrient exchange.[33,34] Failure of spiral artery conversion renders these vessels susceptible to adrenergic stimulation and vasoconstriction,[35,36] resulting in fluctuations in intervillous PaO_2 and placental hypoxia−reperfusion injury. Failure of CT endovascular invasion also results in retention of a "functional sphincter," an innervated stricture point at the junction of the uterine mucosa, predisposing to hypoxia, reperfusion injury, and oxidative stress.[37] Aberrant development of the fetal vascular tree within the placenta, as a consequence of dysregulation of the angiogenic and antiangiogenic factors at the maternal−fetal interface,[38−40] further compromises placental function[41−43] and has been implicated in the development of preeclampsia, fetal growth restriction (FGR), gestational diabetes mellitus, placental abruption, preterm labor, and intrapartum fetal compromise (IFC).[44−49]

Effect of Uterine Contractions on Uteroplacental Perfusion

Uterine contractions during term labor result in a rise in intrauterine pressure of up to 25−70 mm Hg,[50] compromising
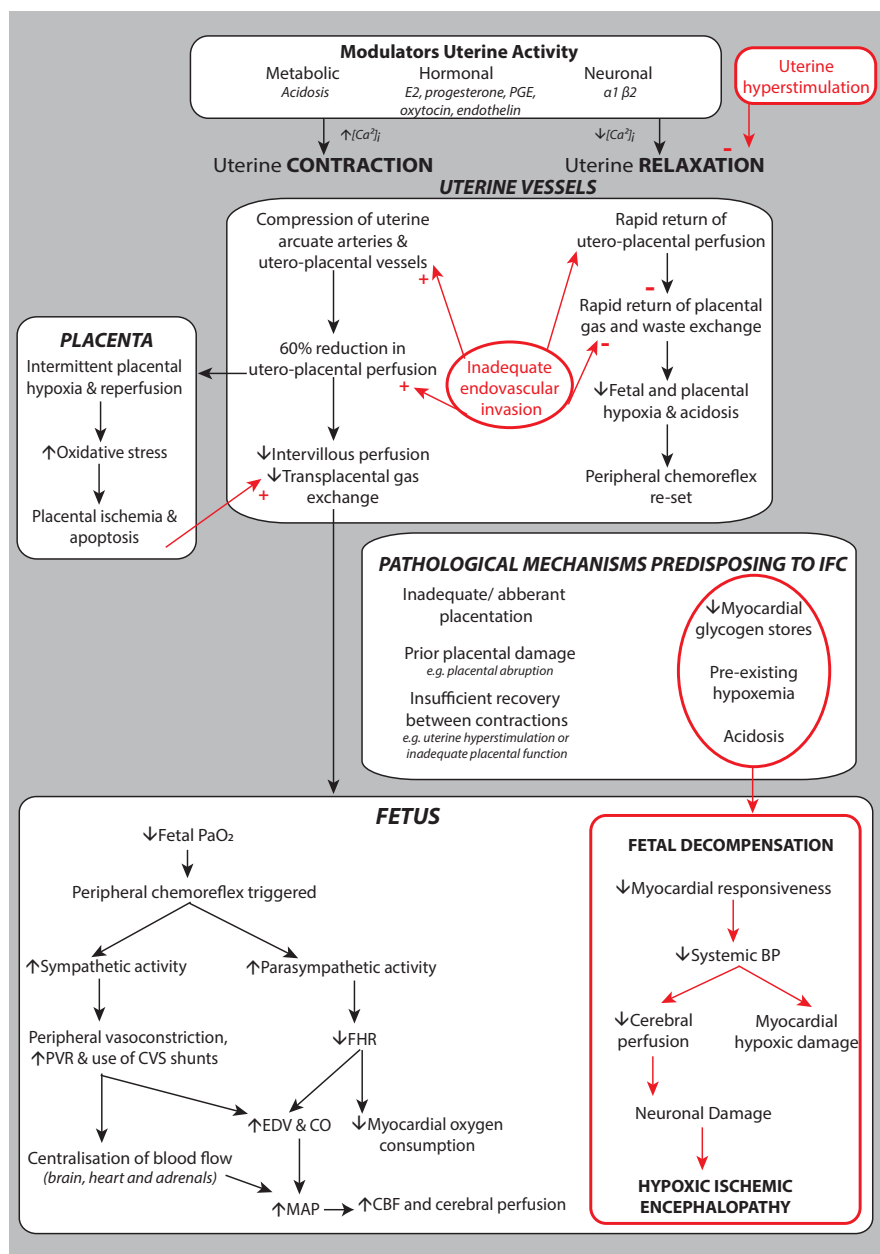
placental perfusion[51] and oxygenation.[52] Because of a reduction in uteroplacental perfusion, intermittent placental hypoxia, reperfusion injury, and oxidative stress occurs, with accelerated trophoblast apoptosis and enhanced endoplasmic reticulum stress.[53,54] In vitro and in vivo studies have demonstrated that repeated ischemia−reperfusion events, as seen in labor, result in a substantial decline in placental mRNA and PlGF levels, which in turn further activates inflammatory cytokine pathways.[55−57] Placentae that are at greatest risk of ischemia−reperfusion injury are those with aberrant conversion of spiral arteries, resulting in narrower vessels with luminal atherosclerotic deposits and retention of vascular innervation and vasoreactivity.[36,58,59]

Impact of Labor on the Fetus

Although uterine contractions result in a decline in fetal PaO_2 by approximately 25%,[60] the majority of appropriately grown, healthy, term fetuses are able to withstand the effects of this over a prolonged period of time. Indeed, normal fetuses can cope with a reduction in PaO_2 of up to 50% (from a PaO_2 above 20 mm Hg to as low as 10−12 mm Hg)[61,62] because of their high myocardial glycogen stores,[63,64] the presence of vascular shunts, the increased oxygen affinity of HbF, and near-maximal basal cardiac output.[65,66] The cornerstone of the fetal defense against hypoxic injury lies in the peripheral chemoreflex, triggered in response to fetal hypoxia when uteroplacental perfusion declines by more than 50%.[67,68] This has the sole aim of rapidly reducing oxygen consumption and centralizing blood flow to the critical organs needed for preservation of life and sensitive to hypoxic injury (the brain, heart, and adrenal glands). The fetal adaptations, including the peripheral chemoreflex, to transient hypoxia are summarized in Figure 1.

Acute hypoxemia, detected by the carotid body chemoreceptors, stimulates the brain stem to increase both the parasympathetic and sympathetic outflow.[69,70] Parasympathetic tone predominates,[71] resulting in a

FIGURE 1
Consequences of uterine contractions, fetal adaptions, and effect of intrapartum fetal compromise

Modulators Uterine Activity

Metabolic	Hormonal	Neuronal
Acidosis	*E2, progesterone, PGE, oxytocin, endothelin*	*α1 β2*

Uterine **hyperstimulation**

$\uparrow[Ca^2]_i$ → Uterine **CONTRACTION** $\downarrow[Ca^2]_i$ → Uterine **RELAXATION** −

UTERINE VESSELS

Compression of uterine arcuate arteries & utero-placental vessels +

Rapid return of utero-placental perfusion −

Rapid return of placental gas and waste exchange −

60% reduction in utero-placental perfusion +

Inadequate endovascular invasion +

$\downarrow$Fetal and placental hypoxia & acidosis

PLACENTA

Intermittent placental hypoxia & reperfusion

$\uparrow$Oxidative stress

Placental ischemia & apoptosis

$\downarrow$Intervillous perfusion $\downarrow$Transplacental gas exchange +

Peripheral chemoreflex re-set

PATHOLOGICAL MECHANISMS PREDISPOSING TO IFC

Inadequate/ abberant placentation

Prior placental damage
e.g. placental abruption

Insufficient recovery between contractions
e.g. uterine hyperstimulation or inadequate placental function

$\downarrow$Myocardial glycogen stores

Pre-existing hypoxemia

Acidosis

FETUS

$\downarrow$Fetal PaO$_2$

Peripheral chemoreflex triggered

$\uparrow$Sympathetic activity $\uparrow$Parasympathetic activity

Peripheral vasoconstriction, $\uparrow$PVR & use of CVS shunts

$\downarrow$FHR

Centralisation of blood flow *(brain, heart and adrenals)*

$\uparrow$EDV & CO $\downarrow$Myocardial oxygen consumption

$\uparrow$MAP → $\uparrow$CBF and cerebral perfusion

FETAL DECOMPENSATION

$\downarrow$Myocardial responsiveness

$\downarrow$Systemic BP

$\downarrow$Cerebral perfusion   Myocardial hypoxic damage

Neuronal Damage

HYPOXIC ISCHEMIC ENCEPHALOPATHY

Illustrated are the effects of uterine contractions upon the uterine vessels, myometrium, placenta, and fetus with a schematic of the peripheral chemo-reflex and the processes/pathologies that interfere with the fetal protective mechanisms and result in hypoxic injury to the fetus.

BP, *blood pressure*; [Ca^{2+}]$_i$, *intracellular calcium*; CBF, *cerebral blood flow*; CO, *cardiac output*; CVS, *cardiovascular system*; E$_2$, *estrogen*; EDV, *end-diastolic volume (cardiac)*; FHR, *fetal heart rate*; IFC, *intrapartum fetal compromise*; MAP, *mean arterial pressure*; PaO$_2$, *partial pressure of oxygen*; PGE, *prostaglandin E$_2$ and F$_2$*; PVR, *peripheral vascular resistance*; ROS, *reactive oxygen species*.

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consumption as well as allowing increased transit time of red cells through tissue beds (including the placenta), thereby permitting increased oxygen extraction from HbF and transplacental oxygen transfer to the fetal circulation.[73] Increased sympathetic outflow induces profound peripheral vasoconstriction, resulting in hypertension and centralization of blood flow to critical organs as well as balancing the parasympathetic effects with a positive chronotropic effect, leading to a partial recovery in FHR.[74,75] Furthermore, peripheral vasoconstriction increases the descending aortic pressure, increasing right ventricular afterload that in turn encourages passage of blood from the right atrium, through the foramen ovale, into the left atrium and thereafter the left ventricle,[76,77] causing an increase in blood flow into the ascending aorta and cerebral and coronary circulations.[78,79]

The initial neuronal triggered peripheral vasoconstriction is then maintained by humoral factors, including adrenal catecholamines, arginine vasopressin, cortisol, angiotensin II, and neuropeptide Y,[80–84] which prolong the redistribution of cardiac output, thus maintaining perfusion to critical organs.

In addition, acute hypoxia stimulates an increase in plasma adenosine[85] and to a lesser extent nitric oxide[86,87] and prostinoids.[88] These potent vasodilators further increase cerebral blood flow independent of the centralization of cardiac output,[85,89] with adenosine accounting for more than one-half of this increase.[90]

With uterine relaxation, there is rapid return of efficient placental gas exchange, restoring fetal PaO$_2$ levels and removing lactate and carbon dioxide.[91] In addition, the fetus is able to efficiently metabolize lactate (by oxidation and conversion to nonessential amino acids and lipids),[92,93] rapidly reversing the metabolic acidosis that occurs during the preceding contraction. These processes allow the autonomic fetal response to be reactivated during the next contraction, ensuring protection from the repeated hypoxic episodes that characterize labor.[74,91]

decrease in the fetal heart rate (FHR), prolonging end-diastolic ventricular filling time, and subsequently end-diastolic volume. The greater ventricular stretch increases sarcomere length, tension, and contractility (Frank–Starling mechanism), maintaining fetal cardiac output despite the decline in FHR.[72] In addition, the reduction in FHR reduces myocardial oxygen

When and why does IFC occur?

It has now clear that fetal decompensation in labor occurs because of the infant's inability to respond to the peripheral chemoreflex to maintain cardiac output.[74,94] IFC may occur when there is inadequate reperfusion time between contractions (eg, during uterine hyperstimulation) or when there is appropriate reperfusion time but suboptimal placental function to allow adequate oxygen transfer to the fetus.[95,96]

Impaired placental development and function renders the fetus vulnerable to intrapartum hypoxia through several mechanisms. First, a greater reduction in uteroplacental perfusion occurs for any rise in intrauterine pressure due to the smaller surface area of the unconverted spiral arteries. Consequently, the degree of fetal hypoxia is greater with each contraction than that which occurs in a fetus with a normally developed and functioning placenta. Furthermore, inadequate placental function is associated with the progressive development of severe fetal acidosis, even with adequate time between contractions, due to an inability to correct the impaired gas exchange between contractions.[97,98]

Women with pre-labor placental dysfunction are more likely to develop IFC. These fetuses are less likely to withstand intrapartum hypoxia due to lower glycogen stores before the onset of labor, limiting their ability to transition to anaerobic metabolism.[99] As even short periods of hypoxia can quickly deplete cerebral and cardiac glycogen by up to 80%,[64] any limitation in placental transfer of nutrients and oxygen renders these fetuses vulnerable to IFC and injury. Progressive hypoxia in labor results in a further reduction of myocardial glycogen stores, impaired cardiac function,[100,101] and, ultimately, profound systemic hypotension and irreversible multiorgan injury.[63,64] Cardiac function is further aggravated by the associated systemic hypotension, limiting coronary blood flow and causing subendocardial myocardial injury.[102] Jones et al[103] recently demonstrated that infants with HIE have elevated troponin-T levels, a marker of myocardial cell death. As

myocardial dysfunction progresses with worsening cerebral and in particular brain stem hypoxia, the fetal parasympathetic response may fail altogether.

The magnitude of the hypoxic insult correlates with the fetal response. Siristatidis et al[104] demonstrated that the "brain-sparing" response is only activated when fetal PaO_2 falls below 37%. However, if the PaO_2 falls below 30% for more than 2 minutes, this response fails altogether and significantly increases the risk of adverse perinatal outcomes.[105]

The impact of intrapartum hypoxic injury

The fetus adapts to hypoxia by preferentially redistributing its cardiac output, mediated by neuroendocrine mechanisms, to its coronary arteries, adrenal glands (for production of catecholamines critical for sustaining circulation),[104] and brain. Occasionally, if the hypoxic insult is severe or prolonged enough, these protective mechanisms fail, and profound multiorgan injury or death can occur.

Hypoxic ischemic encephalopathy. The fetal brain is particularly sensitive to hypoxic injury and oxidative stress due to its high rate of oxygen consumption, lack of glucose stores (therefore all cellular events that are adenosine triphosphate and oxygen dependent rapidly fail), high lipid content (rendering neurons susceptible to lipid peroxidation in an autocatalytic fashion triggered by oxidative stress, leading to structural and function damage),[106,107] and relatively low concentrations and activity of antioxidant enzymes.[108,109] HIE is defined as neonatal encephalopathy (cerebral obtundation with disturbed neurological function)[110] secondary to systemic hypoxia and reduced cerebral perfusion, resulting in ischemic injury that may be focal or diffuse.[111,112] In one study, 51% of neonates with moderate or severe encephalopathy died or developed cerebral palsy).[113]

The mechanisms of hypoxic cerebral damage are complex and not entirely mediated by the initial hypoxic insult but are compounded by injuries occurring

during the reperfusion phase[114] due to toxicity from reactive oxygen species and excessive stimulation of N-methyl-D-aspartate-type glutamate receptors.[115,116] Indeed, the severity of the secondary injury occurring during the reperfusion phase correlates best with the severity of neurodevelopmental disability at ages 1 and 4 years.[117] There is a strong association between hypotension and hypoxia with fetal injury, particularly neuronal damage and fetal death.[113] During hypoxia, blood flow to the cerebral hemispheres is reduced, whereas perfusion to the basal ganglia, thalamus, and brainstem is increased.[118] Animal studies have demonstrated that episodes of intermittent hypoxia accompanied by recurrent fetal hypotension cause neuronal loss in the "watershed" zones of the brain (the parasagittal sinus, cerebellar neocortex, and the dorsal horn of the hippocampus).[119,120] By comparison, hypoxia without hypotension predisposes to cerebellar injury.[121] Animal studies suggest that, even if the total duration of hypoxia is the same, repeated severe episodes cause greater neurologic injury than a single severe prolonged event.[122] This is consistent with recent evidence showing that the FHR deceleration area of the cardiotocograph (ie, a composite of duration and severity) was most discriminative of acidemia in term infants.[123] In addition, the pattern of neuronal damage is further influenced by the pre-labor metabolic and growth status of the fetus,[124] as well as metabolic and nutritional status of the mother.[125]

Noncerebral consequences of intrapartum hypoxia. After the brain, the renal system is the most common organ system to be injured following severe intrapartum hypoxia, with up to 64% of hypoxic term infants developing renal dysfunction usually secondary to acute tubular necrosis.[126–128] Severely hypoxic infants often require dialysis to support renal function, with an associated mortality rate of between 14% and 70%.[129,130]

Between 25% and 50% of hypoxic infants experience pulmonary complications[131] and up to 20% require mechanical ventilation.[132] Both hypoxia

and hyperoxia[133] (from oxygen therapy and ventilation in the neonatal period) impair alveolar development[134] and predispose to persistent pulmonary hypertension and reactive airway disease, which may persist into adulthood.[135]

Cardiac complications occur in up to 29% of infants with severe intrapartum hypoxia with evidence of myocardial ischemia on electrocardiogram seen in almost 1 in 5 cases.[131] Other organ systems, including hepatic (35%) and gastrointestinal (5%), may be affected. More than one-half of infants with HIE have multiorgan dysfunction.[131,135] There are many factors that influence the severity of neonatal morbidity following intrauterine hypoxia as well as our ability to predict the likelihood of hypoxia-related complications.[135,136] Low et al[137] demonstrated that although the range and severity of neonatal complications increased with the degree of metabolic acidosis, there was a great deal of heterogeneity between fetuses, a likely reflection of the nature and length of asphyxial event.

Pre-labor identification of the "at-risk" fetus

There is now evidence that some apparently normally grown fetuses have circulatory changes including cerebral redistribution similar to that seen in FGR. These fetuses are particularly vulnerable to intrapartum hypoxia and compromise.[138-140]

Low birth weight at term is a major risk factor for emergency operative birth for IFC, perinatal death, and serious neonatal morbidity even in low-risk pregnancies,[141] partly due to the proportion of small for gestational age (SGA) babies that are growth restricted. As not all growth-restricted fetuses are SGA, parameters other than standard biometry are required to identify these at-risk infants before birth. Cochrane reviews do not support the use of either routine late pregnancy ultrasound or umbilical artery Doppler assessment in low-risk populations.[142] However, these reviews are limited by small sample size, use of surrogate outcomes, and most importantly, ultrasound scans that were often performed too remote from term,

thereby potentially missing late-onset growth restriction.

More recently, the fetal cerebroplacental ratio (CPR) (ratio of the middle cerebral artery pulsatility index to the umbilical artery pulsatility index) has been proposed as a proxy for intrauterine growth with a low CPR indicative of suboptimal fetal growth. A low CPR (variably defined as <1.0, <5th centile, <10th centile, or <0.67 Multiples of Median [MoM])[143,144] is associated with a range of adverse perinatal outcomes, including neonatal intensive care admission, acidosis, and emergency operative birth for IFC.[145,146] However, despite the broad association with adverse outcomes, the predictive utility of the CPR, particularly in a non-SGA cohort at term, remains modest, and caution should be exercised before incorporating its routine use into clinical care.[147]

Biochemical markers. Low PAPP-A levels are indicative of failure of trophoblast invasion and placental dysfunction[22] and associated with an increased risk of FGR, preeclampsia, intrauterine fetal demise, placental abruption, preterm birth, emergency cesarean delivery for IFC, and neonatal acidosis.[24,26] Although low maternal PlGF levels in the third trimester have been shown to be associated with IFC and adverse neonatal outcomes,[148,149] the evidence is conflicting with another recent study, suggesting that it did not predict cesarean birth for fetal compromise.[150]

Identification of intrapartum fetal compromise

Despite concerted efforts to develop accurate techniques for the identification of intrapartum fetal hypoxia, to date all techniques currently in clinical practice have poor positive predictive values.[151] Reviews of conventional antepartum cardiotocography (CTG), computerized FHR analysis, or intermittent auscultation have concluded that they do not result in improved perinatal outcomes.[152,153] The CTG has poor characteristics as a test: interpretation is subjective, it has poor intra- and interobserver agreement, and lacks discriminatory power in identifying truly

hypoxic fetuses.[154] Despite these limitations, it remains the mainstay for intrapartum fetal monitoring despite having a false-positive rate as high as 99.8%.[155,156] Although the use of intrapartum electronic FHR monitoring has resulted in a reduction in the incidence of neonatal seizures, there is no improvement in perinatal death or cerebral palsy rates despite an increase in operative births.[155] The implementation of CTG monitoring use and interpretation guidelines has nevertheless reduced the incidence of HIE.[157-160] However, the use of computerized CTG analysis software has failed to demonstrate any significant improvement in maternal or neonatal outcomes compared with standard FHR monitoring.[161,162]

Assessment of fetal wellbeing using ST-segment waveform analysis from the fetal electrocardiogram[163,164] has been proposed as an adjunct to conventional FHR monitoring. Westgate et al[165] investigated the use of ST-segment analysis in animal models and demonstrated that although the T/QRS ratio indicated hypoxic stress, it correlated poorly with the severity of fetal hypoxia or hypotension. Several randomized controlled trials and meta-analyses have produced conflicting results, with the most recent randomized controlled trial not demonstrating any improvement in either neonatal outcomes or reduction in operative birth rates.[164] A recent observational study showed that the implementation of intrapartum ST-segment waveform resulted in a substantial reduction in rates of umbilical artery metabolic acidosis as well as a significant reduction in operative birth rates, fetal blood sampling, and incidence of neonatal encephalopathy.[166]

Fetal pulse oximetry (FPO) was developed as an adjunct to electronic FHR monitoring, particularly in the context of a nonreassuring FHR pattern. Fetal PO_2 saturations less than 30% are considered abnormal and corelate with hypoxic injury.[104] In May 2000, the Food and Drug Administration granted approval for use of FPO[167] as an adjunct to FHR monitoring based on a single randomized controlled trial that showed a significant reduction in cesarean section

(CS) for IFC.[168] However in 2006, a large, multicenter randomized controlled trial demonstrated that FPO as an adjunct to FHR monitoring did not reduce the rate of CS for any indication.[169] An updated Cochrane review in 2013 of 7 published trials demonstrated that although FPO did not impact overall CS rates compared with FHR monitoring alone, there was a reduction in CS for IFC.[170]

Intrapartum assessment of fetal scalp pH or lactate has not resulted in a decline in operative birth rates for IFC, neonatal acidosis, or adverse neonatal outcomes compared with the use of FHR monitoring alone.

Conclusion

Although the etiology of IFC is multifactorial, placental dysfunction and a mismatch between its functional ability and the metabolic requirements of fetus during labor is causative in the majority of cases. Labor is characterized by repeated transient episodes of fetal hypoxia that, under normal circumstances, an appropriately grown fetus with normal or minimal placental dysfunction is able to tolerate. However, when there is pre-existing placental dysfunction, inadequate uterine relaxation between contractions, or if the fetus is growth restricted with suboptimal metabolic reserves, intrapartum fetal hypoxia can ensue. In extreme cases, this can result in myocardial injury, systemic hypotension, cerebral hypoperfusion, and neuronal damage. Neonatal encephalopathy can have catastrophic consequences, with 1 in 2 infants either having significant neurodevelopmental delay, cerebral palsy, or death by the age of 2.

The challenges in this field are first, the development of a reliable pre-labor test that accurately identifies fetuses at risk of intrapartum compromise, second to develop new or refine current intrapartum techniques for fetal monitoring, and finally a prenatal or intrapartum treatment that can either prevent the development of intrapartum hypoxia or mitigate some of its perinatal complications. Accompanying these should be safe intrapartum care provided by trained caregivers. ∎

REFERENCES

1. Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet 2014;384:189–205.
2. Lawn J, Shibuya K, Stein C. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bull World Health Organ 2005;83:409–17.
3. McIntyre S, Taitz D, Keogh J, Goldsmith S, Badawi N, Blair E. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. Dev Med Child Neurol 2013;55:499–508.
4. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1859–922.
5. Low JA, Pickersgill H, Killen H, Derrick EJ. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol 2001;184:724–30.
6. Janbu T, Nesheim BI. Uterine artery blood velocities during contractions in pregnancy and labour related to intrauterine pressure. Br J Obstet Gynaecol 1987;94:1150–5.
7. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am J Pathol 2000;157: 2111–22.
8. Burton GJ. Oxygen, the Janus gas; its effects on human placental development and function. J Anatomy 2009;215:27–35.
9. Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development by oxygen tension. Science 1997;277:1669–72.
10. Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: the Boyd collection revisited. Am J Obstet Gynecol 1999;181:718–24.
11. Zhou Y, Fisher SJ, Janatpour M, et al. Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? J Clin Invest 1997;99:2139–51.
12. Maltepe E, Bakardjiev AI, Fisher SJ. The placenta: transcriptional, epigenetic, and physiological integration during development. J Clin Invest 2010;120:1016–25.
13. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006;27: 939–58.
14. Lyall F. Priming and remodelling of human placental bed spiral arteries during pregnancy—a review. Placenta 2005;26(suppl A):S31–6.
15. Brosens I. A Study of the spiral arteries of the decidua basalis in normotensive and hypertensive pregnancies. J Obstet Gynaecol Br Commonw 1964;71:222–30.

16. Red-Horse K, Zhou Y, Genbacev O, et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. J Clin Invest 2004;114:744–54.
17. Ahmed A. Angiogenic growth factors in pregnancy. In: Aplin JD KP, Schaaps JP, Foidart JM, eds. Trophoblast research, early pregnancy. Vol. 9. New York: University of Rochester Press; 1997. p. 215–58.
18. Ahmed A, Li XF, Dunk C, Whittle MJ, Rushton DI, Rollason T. Colocalisation of vascular endothelial growth factor and its Flt-1 receptor in human placenta. Growth Factors 1995;12:235–43.
19. McKinnon T, Chakraborty C, Gleeson LM, Chidiac P, Lala PK. Stimulation of human extravillous trophoblast migration by IGF-II is mediated by IGF type 2 receptor involving inhibitory G protein(s) and phosphorylation of MAPK. J Clin Endocrinol Metab 2001;86: 3665–74.
20. Lacey H, Haigh T, Westwood M, Aplin JD. Mesenchymally-derived insulin-like growth factor 1 provides a paracrine stimulus for trophoblast migration. BMC Dev Biol 2002;2:5.
21. Bonno M, Oxvig C, Kephart GM, et al. Localization of pregnancy-associated plasma protein-A and colocalization of pregnancy-associated plasma protein-A messenger ribonucleic acid and eosinophil granule major basic protein messenger ribonucleic acid in placenta. Lab Invest 1994;71:560–6.
22. Qiu Q, Bell M, Lu X, et al. Significance of IGFBP-4 in the development of fetal growth restriction. J Clin Endocrinol Metab 2012;97: E1429–39.
23. Johnson MR, Riddle AF, Grudzinskas JG, Sharma V, Collins WP, Nicolaides KH. Reduced circulating placental protein concentrations during the first trimester are associated with preterm labour and low birth weight. Hum Reprod 1993;8:1942–7.
24. Smith GC, Shah I, Crossley JA, et al. Pregnancy-associated plasma protein A and alpha-fetoprotein and prediction of adverse perinatal outcome. Obstet Gynecol 2006;107: 161–6.
25. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. Prenat Diagn 2008;28:7–10.
26. Uccella S, Colombo GF, Bulgheroni CM, et al. First-trimester maternal serum screening and the risk for fetal distress during labor. Am J Obstet Gynecol 2009;201:166 e161–6.
27. Demir R, Kayisli UA, Cayli S, Huppertz B. Sequential steps during vasculogenesis and angiogenesis in the very early human placenta. Placenta 2006;27:535–9.
28. Cao Y, Linden P, Shima D, Browne F, Folkman J. In vivo angiogenic activity and hypoxia induction of heterodimers of placenta growth factor/vascular endothelial growth factor. J Clin Invest 1996;98:2507–11.
29. Khaliq A, Dunk C, Jiang J, et al. Hypoxia down-regulates placenta growth factor,

whereas fetal growth restriction up-regulates placenta growth factor expression: molecular evidence for "placental hyperoxia" in intrauterine growth restriction. Lab Invest 1999;79:151–70.

30. Shore VH, Wang TH, Wang CL, Torry RJ, Caudle MR, Torry DS. Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. Placenta 1997;18:657–65.

31. Desai J, Holt-Shore V, Torry RJ, Caudle MR, Torry DS. Signal transduction and biological function of placenta growth factor in primary human trophoblast. Biol Reprod 1999;60:887–92.

32. Scifres CM, Nelson DM. Intrauterine growth restriction, human placental development and trophoblast cell death. J Physiol 2009;587:3453–8.

33. Savasan ZA, Goncalves LF, Bahado-Singh RO. Second-and third-trimester biochemical and ultrasound markers predictive of ischemic placental disease. Paper presented at: Seminars in perinatology 2014.

34. Burton GJ, Jones CJ. Syncytial knots, sprouts, apoptosis, and trophoblast deportation from the human placenta. Taiwan J Obstet Gynecol 2009;48:28–37.

35. Adamsons K, Mueller-Heubach E, Myers RE. Production of fetal asphyxia in the rhesus monkey by administration of catecholamines to the mother. Am J Obstet Gynecol 1971;109:248–62.

36. Adamsons K, Myers RE. Circulation in the intervillous space; obstetrical considerations in fetal deprivation. In: Gruenwald P, ed. The placenta and its maternal supply line. Effects of insufficiency on the fetus. Lancaster: Medical and Technical Publishing Co. Ltd; 1975. p. 158–77.

37. Brosens JJ, Pijnenborg R, Brosens IA. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. Am J Obstet Gynecol 2002;187:1416–23.

38. Kon K, Fujii S, Kosaka H, Fujiwara T. Nitric oxide synthase inhibition by N(G)-nitro-L-arginine methyl ester retards vascular sprouting in angiogenesis. Microvasc Res 2003;65:2–8.

39. Fisher SJ. The placental problem: linking abnormal cytotrophoblast differentiation to the maternal symptoms of preeclampsia. Reprod Biol Endocrinol 2004;2:53.

40. Zhou Z, Yang XM, Xie YZ, Yin ZY. Vascular endothelial growth factor gene expression regulated by protein kinase C pathway in endothelial cells during hypoxia. Space Med Med Eng (Beijing) 2002;15:322–6.

41. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. Obstet Gynecol 1992;80:283–5.

42. Soothill PW, Nicolaides KH, Rodeck CH, Campbell S. Effect of gestational age on fetal and intervillous blood gas and acid-base values in human pregnancy. Fetal Ther 1986;1:168–75.

43. Talbert DG. Uterine flow velocity waveform shape as an indicator of maternal and placental development failure mechanisms: a model-based synthesizing approach. Ultrasound Obstet Gynecol 1995;6:261–71.

44. Leung DN, Smith SC, To KF, Sahota DS, Baker PN. Increased placental apoptosis in pregnancies complicated by preeclampsia. Am J Obstet Gynecol 2001;184:1249–50.

45. Smith SC, Baker PN, Symonds EM. Increased placental apoptosis in intrauterine growth restriction. Am J Obstet Gynecol 1997;177:1395–401.

46. Fisher SJ. Why is placentation abnormal in preeclampsia? Am J Obstet Gynecol 2015;213:S115–22.

47. Ananth CV. Ischemic placental disease: a unifying concept for preeclampsia, intrauterine growth restriction, and placental abruption. Paper presented at: Seminars in perinatology 2014.

48. Fisher SJ, McMaster M, Roberts JM. The placenta in normal pregnancy and preeclampsia. In: Taylor RN, Roberts J, Cunningham R, Lindheimer M, eds. Chesley's hypertensive disorders of pregnancy, 4th ed. San Diego: Academic Press; 2015. p. 81–112.

49. Maltepe E, Fisher SJ. Placenta: the forgotten organ. Annu Rev Cell Dev Biol 2015;31:523–52.

50. Allman AC, Genevier ES, Johnson MR, Steer PJ. Head-to-cervix force: an important physiological variable in labour. 1. The temporal relation between head-to-cervix force and intrauterine pressure during labour. Br J Obstet Gynaecol 1996;103:763–8.

51. Borell U, Fernstroem I, Ohlson L, Wiqvist N. Influence of uterine contractions on the utero-placental blood flow at term. Am J Obstet Gynecol 1965;93:44–57.

52. Sato M, Noguchi J, Mashima M, Tanaka H, Hata T. 3D power Doppler ultrasound assessment of placental perfusion during uterine contraction in labor. Placenta 2016;45:32–6.

53. Sinding M, Peters DA, Frokjaer JB, Christiansen OB, Uldbjerg N, Sorensen A. Reduced placental oxygenation during subclinical uterine contractions as assessed by BOLD MRI. Placenta 2016;39:16–20.

54. Cindrova-Davies T, Yung HW, Johns J, et al. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. Am J Pathol 2007;171:1168–79.

55. Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung HW. Placental endoplasmic reticulum stress negatively regulates transcription of placental growth factor via ATF4 and ATF6beta: implications for the pathophysiology of human pregnancy complications. J Pathol 2016;238:550–61.

56. Many A, Roberts JM. Increased xanthine oxidase during labour—implications for oxidative stress. Placenta 1997;18:725–6.

57. Li H, Gu B, Zhang Y, Lewis DF, Wang Y. Hypoxia-induced increase in soluble Flt-1 production correlates with enhanced oxidative stress in trophoblast cells from the human placenta. Placenta 2005;26:210–7.

58. Dunn L, Flatley C, Kumar S. Changes in maternal placental growth factor levels during term labour. Placenta 2018;61:11–6.

59. Fleischer A, Anyaegbunam AA, Schulman H, Farmakides G, Randolph G. Uterine and umbilical artery velocimetry during normal labor. Am J Obstet Gynecol 1987;157:40–3.

60. Brar HS, Platt LD, DeVore GR, Horenstein J, Medearis AL. Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. Am J Obstet Gynecol 1988;158:952–6.

61. Jansen CA, Krane EJ, Thomas AL, et al. Continuous variability of fetal PO2 in the chronically catheterized fetal sheep. Am J Obstet Gynecol 1979;134:776–83.

62. Giussani DA, Spencer JAD, Hanson MA. Fetal cardiovascular reflex responses to hypoxaemia. Fetal Maternl Med Rev 1994;6:17–37.

63. Jensen A, Garnier Y, Berger R. Dynamics of fetal circulatory responses to hypoxia and asphyxia. Eur J Obstet Gynecol Reprod Biol 1999;84:155–72.

64. Dawes GS, Mott JC, Shelley HJ. The importance of cardiac glycogen for the maintenance of life in foetal lambs and newborn animals during anoxia. J Physiol 1959;146:516–38.

65. Shelley HJ. Glycogen reserves and their changes at birth and in anoxia. Br Med Bull 1961;17:137–43.

66. Harding R, Bocking AD. Fetal growth and development. Cambridge: Cambridge University Press; 2001.

67. Rudolph AM. Distribution and regulation of blood flow in the fetal and neonatal lamb. Circ Res 1985;57:811–21.

68. Ross MG, Jessie M, Amaya K, et al. Correlation of arterial fetal base deficit and lactate changes with severity of variable heart rate decelerations in the near-term ovine fetus. Am J Obstet Gynecol 2013;208:285 e281–6.

69. Itskovitz J, LaGamma EF, Rudolph AM. Heart rate and blood pressure responses to umbilical cord compression in fetal lambs with special reference to the mechanism of variable deceleration. Am J Obstet Gynecol 1983;147:451–7.

70. Itskovitz J, LaGamma EF, Bristow J, Rudolph AM. Cardiovascular responses to hypoxemia in sinoaortic-denervated fetal sheep. Pediatr Res 1991;30:381–5.

71. Giussani DA, Spencer JA, Moore PJ, Bennet L, Hanson MA. Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep. J Physiol 1993;461:431–49.

72. Court DJ, Parer JT, Block BS, Llanos AJ. Effects of beta-adrenergic blockade on blood flow distribution during hypoxaemia in fetal sheep. J Dev Physiol 1984;6:349–58.

73. Anderson PA, Glick KL, Killam AP, Mainwaring RD. The effect of heart rate on in

utero left ventricular output in the fetal sheep. J Physiol 1986;372:557–73.

74. Bennet L, Gunn AJ. The fetal heart rate response to hypoxia: insights from animal models. Clin Perinatol 2009;36:655–72.

75. Galinsky R, Jensen EC, Bennet L, et al. Sustained sympathetic nervous system support of arterial blood pressure during repeated brief umbilical cord occlusions in near-term fetal sheep. Am J Physiol Regul Integr Comp Physiol 2014;306:R787–95.

76. Giussani DA. The fetal brain sparing response to hypoxia: physiological mechanisms. J Physiol 2016;594:1215–30.

77. Griffin D, Bilardo K, Masini L, et al. Doppler blood flow waveforms in the descending thoracic aorta of the human fetus. Br J Obstet Gynaecol 1984;91:997–1006.

78. Akalin-Sel T, Nicolaides KH, Peacock J, Campbell S. Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. Obstet Gynecol 1994;84: 439–44.

79. Arbeille P, Maulik D, Fignon A, et al. Assessment of the fetal PO2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. Ultrasound Med Biol 1995;21:861–70.

80. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br J Obstet Gynaecol 1986;93:471–5.

81. Broughton Pipkin F, Lumbers ER, Mott JC. Factors influencing plasma renin and angiotensin II in the conscious pregnant ewe and its foetus. J Physiol 1974;243:619–36.

82. Giussani DA, McGarrigle HH, Spencer JA, Moore PJ, Bennet L, Hanson MA. Effect of carotid denervation on plasma vasopressin levels during acute hypoxia in the late-gestation sheep fetus. J Physiol 1994;477:81–7.

83. Jones CT, Robinson RO. Plasma catecholamines in foetal and adult sheep. J Physiol 1975;248:15–33.

84. Fletcher AJ, Edwards CM, Gardner DS, Fowden AL, Giussani DA. Neuropeptide Y in the sheep fetus: effects of acute hypoxemia and dexamethasone during late gestation. Endocrinology 2000;141:3976–82.

85. Fletcher AJ, Gardner DS, Edwards CM, Fowden AL, Giussani DA. Development of the ovine fetal cardiovascular defense to hypoxemia towards full term. Am J Physiol Heart Circ Physiol 2006;291:H3023–34.

86. Blood AB, Hunter CJ, Power GG. The role of adenosine in regulation of cerebral blood flow during hypoxia in the near-term fetal sheep. J Physiol 2002;543:1015–23.

87. Thakor AS, Richter HG, Kane AD, et al. Redox modulation of the fetal cardiovascular defence to hypoxaemia. J Physiol 2010;588: 4235–47.

88. van Bel F, Sola A, Roman C, Rudolph AM. Role of nitric oxide in the regulation of the cerebral circulation in the lamb fetus during normoxemia and hypoxemia. Biol Neonate 1995;68:200–10.

89. Nishida N, Blood AB, Hunter CJ, et al. Role of prostanoids in the regulation of cerebral blood flow during normoxia and hypoxia in the fetal sheep. Pediatr Res 2006;60:524–9.

90. Giussani DA, Gardner DS, Cox DT, Fletcher AJ. Purinergic contribution to circulatory, metabolic, and adrenergic responses to acute hypoxemia in fetal sheep. Am J Physiol Regul Integr Comp Physiol 2001;280:R678–85.

91. Park TS, Van Wylen DG, Rubio R, Berne RM. Increased brain interstitial fluid adenosine concentration during hypoxia in newborn piglet. J Cereb Blood Flow Metab 1987;7:178–83.

92. Bennet L, Westgate JA, Liu YC, Wassink G, Gunn AJ. Fetal acidosis and hypotension during repeated umbilical cord occlusions are associated with enhanced chemoreflex responses in near-term fetal sheep. J Appl Physiol (1985) 2005;99:1477–82.

93. Carter BS, Moores RR Jr, Teng C, Meschia G, Battaglia FC. Main routes of plasma lactate carbon disposal in the midgestation fetal lamb. Biol Neonate 1995;67:295–300.

94. Bartelds B, Knoester H, Smid GB, et al. Perinatal changes in myocardial metabolism in lambs. Circulation 2000;102:926–31.

95. Galinsky R, Lear CA, Yamaguchi K, et al. Cholinergic and beta-adrenergic control of cardiovascular reflex responses to brief repeated asphyxia in term-equivalent fetal sheep. Am J Physiol Regul Integr Comp Physiol 2016;311: R949–56.

96. Lear CA, Wassink G, Westgate JA, et al. The peripheral chemoreflex: indefatigable guardian of fetal physiological adaptation to labour. J Physiol 2018;596:5611–23.

97. Bakker PC, Kurver PH, Kuik DJ, Van Geijn HP. Elevated uterine activity increases the risk of fetal acidosis at birth. Am J Obstet Gynecol 2007;196:313 e311–6.

98. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. Am J Obstet Gynecol 2008;199: 34 e31–5.

99. Wassink G, Bennet L, Davidson JO, Westgate JA, Gunn AJ. Pre-existing hypoxia is associated with greater EEG suppression and early onset of evolving seizure activity during brief repeated asphyxia in near-term fetal sheep. PLoS One 2013;8:e73895.

100. Westgate JA, Wassink G, Bennet L, Gunn AJ. Spontaneous hypoxia in multiple pregnancies is associated with early fetal decompensation and enhanced T-wave elevation during brief repeated cord occlusion in near-term fetal sheep. Am J Obstet Gynecol 2005;193:1526–33.

101. Fisher DJ. Acidaemia reduces cardiac output and left ventricular contractility in conscious lambs. J Dev Physiol 1986;8:23–31.

102. Mott JC. The ability of young mammals to withstand total oxygen lack. Br Med Bull 1961;17:144–8.

103. Jones R, Heep A, Odd D. Biochemical and clinical predictors of hypoxic-ischemic encephalopathy after perinatal asphyxia. J Matern Fetal Neonatal Med 2018;31:791–6.

104. Siristatidis C, Salamalekis E, Kassanos D, Loghis C, Creatsas G. Evaluation of fetal intrapartum hypoxia by middle cerebral and umbilical artery Doppler velocimetry with simultaneous cardiotocography and pulse oximetry. Arch Gynecol Obstet 2004;270:265–70.

105. Gunn AJ, Maxwell L, De Haan HH, et al. Delayed hypotension and subendocardial injury after repeated umbilical cord occlusion in near-term fetal lambs. Am J Obstet Gynecol 2000;183:1564–72.

106. Bloom SL, Swindle RG, McIntire DD, Leveno KJ. Fetal pulse oximetry: duration of desaturation and intrapartum outcome. Obstet Gynecol 1999;93:1036–40.

107. Stockwell BR, Angeli JPF, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell 2017;171:273–85.

108. Cuypers A, Plusquin M, Remans T, et al. Cadmium stress: an oxidative challenge. Biometals 2010;23:927–40.

109. Miller SL, Wallace EM, Walker DW. Antioxidant therapies: a potential role in perinatal medicine. Neuroendocrinology 2012;96:13–23.

110. McLean C, Ferriero D. Mechanisms of hypoxic-ischemic injury in the term infant. Semin Perinatol 2004;28:425–32.

111. Schendel D. Executive summary: neonatal encephalopathy and neurologic outcome, Report of the American College of Obstetricians and Gynecologists' task force on neonatal encephalopathy. Obstet Gynecol 2014;123: 896–901.

112. Cotten CM, Shankaran S. Hypothermia for hypoxic—ischemic encephalopathy. Exp Rev Obstet Gynecol 2010;5:227–39.

113. Pierrat V, Haouari N, Liska A, et al. Prevalence, causes, and outcome at 2 years of age of newborn encephalopathy: population based study. Arch Dis Child Fetal Neonatal Ed 2005;90:F257–61.

114. Gunn AJ, Bennet L. Fetal hypoxia insults and patterns of brain injury: insights from animal models. Clin Perinatol 2009;36:579–93.

115. Choi DW, Rothman SM. The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. Annu Rev Neurosci 1990;13:171–82.

116. Mishra OP, Delivoria-Papadopoulos M. Cellular mechanisms of hypoxic injury in the developing brain. Brain Res Bull 1999;48: 233–8.

117. Roth SC, Baudin J, Cady E, et al. Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. Dev Med Child Neurol 1997;39:718–25.

118. Jensen A, Hohmann M, Kunzel W. Dynamic changes in organ blood flow and oxygen consumption during acute asphyxia in fetal sheep. J Dev Physiol 1987;9:543–59.

119. Gunn AJ, Parer JT, Mallard EC, Williams CE, Gluckman PD. Cerebral histologic

and electrocorticographic changes after asphyxia in fetal sheep. Pediatr Res 1992;31: 486–91.

120. Ikeda T, Murata Y, Quilligan EJ, et al. Physiologic and histologic changes in near-term fetal lambs exposed to asphyxia by partial umbilical cord occlusion. Am J Obstet Gynecol 1998;178:24–32.

121. de Haan HH, Van Reempts JL, Vles JS, de Haan J, Hasaart TH. Effects of asphyxia on the fetal lamb brain. Am J Obstet Gynecol 1993;169:1493–501.

122. Mallard EC, Williams CE, Gunn AJ, Gunning MI, Gluckman PD. Frequent episodes of brief ischemia sensitize the fetal sheep brain to neuronal loss and induce striatal injury. Pediatr Res 1993;33:61–5.

123. Cahill AG, Tuuli MG, Stout MJ, López JD, Macones GA. A prospective cohort study of fetal heart rate monitoring: deceleration area is predictive of fetal acidemia. Am J Obstet Gynecol 2018;218:523. e521-523. e512.

124. Pulgar VM, Zhang J, Massmann GA, Figueroa JP. Mild chronic hypoxia modifies the fetal sheep neural and cardiovascular responses to repeated umbilical cord occlusion. Brain Res 2007;1176:18–26.

125. Hawkins P, Steyn C, McGarrigle HH, et al. Effect of maternal nutrient restriction in early gestation on responses of the hypothalamic-pituitary-adrenal axis to acute isocapnic hypoxaemia in late gestation fetal sheep. Exp Physiol 2000;85:85–96.

126. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr 2005;42:928–34.

127. Perlman JM, Tack ED, Martin T, Shackelford G, Amon E. Acute systemic organ injury in term infants after asphyxia. Am J Dis Child 1989;143:617–20.

128. Mohammed LH, Khairy MA, El-Hussieny NA, Zaazou MH, Aly RM. Multi-organ dysfunction in neonates with hypoxic-ischemic encephalopathy. Med J Cairo University 2010;78(2).

129. Mathew OP, Jones AS, James E, Bland H, Groshong T. Neonatal renal failure: usefulness of diagnostic indices. Pediatrics 1980;65:57–60.

130. Ellis EN, Arnold WC. Use of urinary indexes in renal failure in the newborn. Am J Dis Child 1982;136:615–7.

131. Martin-Ancel A, Garcia-Alix A, Gaya F, Cabanas F, Burgueros M, Quero J. Multiple organ involvement in perinatal asphyxia. J Pediatr 1995;127:786–93.

132. Massaro D, Massaro GD. Invited review: pulmonary alveoli: formation, the "call for oxygen," and other regulators. Am J Physiol Lung Cell Mol Physiol 2002;282:L345–58.

133. Davis RP, Mychaliska GB. Neonatal pulmonary physiology. Paper presented at: Seminars in pediatric surgery 2013.

134. Vogel ER, Britt RD Jr, Trinidad MC, et al. Perinatal oxygen in the developing lung. Can J Physiol Pharmacol 2014;93:119–27.

135. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol 1994;170:1081–7.

136. Parer JT. Effects of fetal asphyxia on brain cell structure and function: limits of tolerance. Comp Biochem Physiol A Mol Integr Physiol 1998;119:711–6.

137. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177: 1391–4.

138. Sabdia S, Greer RM, Prior T, Kumar S. Predicting intrapartum fetal compromise using the fetal cerebro-umbilical ratio. Placenta 2015;36:594–8.

139. Morales-Roselló J, Khalil A. Fetal cerebroplacental ratio and adverse perinatal outcome. J Perinatal Med 2016;44:355.

140. Bligh LN, Alsolai AA, Greer RM, Kumar S. Cerebroplacental ratio thresholds measured within 2 weeks before birth and risk of Cesarean section for intrapartum fetal compromise and adverse neonatal outcome. Ultrasound Obstet Gynecol 2018;52:340–6.

141. Madden JV, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol 2018;218:525. e521-525. e529.

142. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev 2015(6):CD001451.

143. Bligh LN, Al Solai A, Greer RM, Kumar S. Diagnostic performance of cerebroplacental ratio thresholds at term for prediction of low birthweight and adverse intrapartum and neonatal outcomes in a term, low-risk population. Fetal Diagn Ther 2018;43:191–8.

144. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol 2015;213:5–15.

145. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;52:430–41.

146. Prior T, Paramasivam G, Bennett P, Kumar S. Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? Ultrasound Obstet Gynecol 2015;46:460–4.

147. Kumar S, Figueras F, Ganzevoort W, Turner J, McCowan L. Using cerebroplacental ratio in non-SGA infants to predict adverse perinatal outcome: caution is required. Ultrasound Obstet Gynecol 2018;52:427–9.

148. Sherrell H, Dunn L, Clifton V, Kumar S. Systematic review of maternal Placental Growth Factor levels in late pregnancy as a predictor of adverse intrapartum and perinatal outcomes. Eur J Obstet Gynecol Reprod Biol 2018;225: 26–34.

149. Bligh LN, Greer RM, Kumar S. The relationship between maternal placental growth factor levels and intrapartum fetal compromise. Placenta 2016;48:63–7.

150. Ciobanou A, Jabak S, De Castro H, Frei L, Akolekar R, Nicolaides K. Biomarkers of impaired placentation at 35—37 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol 2019;54: 79–86.

151. Low JA. Intrapartum fetal surveillance. Is it worthwhile? Obstet Gynecol Clin North Am 1999;26:725–39.

152. Devane D, Lalor JG, Daly S, McGuire W, Smith V. Cardiotocography versus intermittent auscultation of fetal heart on admission to labour ward for assessment of fetal wellbeing. Cochrane Database Syst Rev 2012;(2): CD005122.

153. Grivell RM, Alfirevic Z, Gyte G, Devane D. Antenatal cardiotocography for fetal assessment. Cochrane Database Syst Rev 2010;1: CD007863.

154. Ayres-de-Campos D, Bernardes J, Costa-Pereira A, Pereira-Leite L. Inconsistencies in classification by experts of cardiotocograms and subsequent clinical decision. BJOG 1999;106: 1307–10.

155. Alfirevic Z, Devane D, Gyte GML. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour (Review). Cochrane Library 2007(4).

156. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 1996;334:613–8.

157. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114:192–202.

158. NICE. Intrapartum care for healthy women and babies, clinical guideline CG190. 2017.

159. RANZCOG. Intrapartum fetal surveillance. Available at: https://ranzcog.edu.au/RANZCOG _SITE/media/RANZCOG-MEDIA/Women%27s %20Health/Statement%20and%20guidelines/ Clinical-Obstetrics/Intrapartum-Fetal-Surveillance-Guideline-Third-edition-Aug-2014.pdf?ext=.pdf. Accessed August 30, 2019.

160. Byford S, Weaver E, Anstey C. Has the incidence of hypoxic ischaemic encephalopathy in Queensland been reduced with improved education in fetal surveillance monitoring? Aust N Z J Obstet Gynaecol 2014;54:348–53.

161. Nunes I, Ayres-de-Campos D, Ugwumadu A, et al. Central fetal monitoring with and without computer analysis: a randomized controlled trial. Obstet Gynecol 2017;129: 83–90.

162. Brocklehurst P, Field D, Greene K, et al. Computerised interpretation of fetal heart rate during labour (INFANT): a randomised controlled trial. Lancet 2017;389:1719–29.

163. Hokegard KH, Eriksson BO, Kjellmer I, Magno R, Rosen KG. Myocardial metabolism in relation to electrocardiographic changes

and cardiac function during graded hypoxia in the fetal lamb. Acta Physiol Scand 1981;113: 1–7.

164. Belfort MA, Saade GR, Thom E, et al. A randomized trial of intrapartum fetal ECG ST-segment analysis. N Engl J Med 2015;373: 632–41.

165. Westgate JA, Bennet L, Brabyn C, Williams CE, Gunn AJ. ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. Am J Obstet Gynecol 2001;184:743–51.

166. Landman AJ, Immink-Duijker ST, Mulder EJ, Koster MP, Xodo S, Visser GH, Groenendaal F, Kwee A. Significant reduction in umbilical artery metabolic acidosis after implementation of intrapartum ST waveform analysis of the fetal electrocardiogram. American journal of obstetrics and gynecology 2019 Feb 28.

167. Food and Drug Administration. Summary minutes: meeting of the Obstetrics and Gynecology Devices Advisory Panel, open session, June 9, 2003. In: 2003.

168. Garite TJ, Dildy GA, McNamara H, et al. A multicenter controlled trial of fetal pulse oximetry in the intrapartum management of non-reassuring fetal heart rate patterns. Am J Obstet Gynecol 2000;183:1049–58.

169. Bloom SL, Spong CY, Thom E, et al. Fetal pulse oximetry and cesarean delivery. N Engl J Med 2006;355:2195–202.

170. East CE, Begg L, Colditz PB, Lau R. Fetal pulse oximetry for fetal assessment in labour. Cochrane Database Syst Rev 2014(10): CD004075.