Intra-partum fetal compromise: Prediction and risk stratification prior to labour

PhD Thesis

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Declaration of originality
I declare that this thesis is my own work. Where other people's work has been used, this has been appropriately referenced.

Peer reviewed publications resulting from this thesis.

Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. Am J Obstet Gynecol. 2013 Feb;208(2):124.e1-6. doi: 10.1016/j.ajog.2012.11.016. Epub 2012 Nov 15.

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Prior T, Mullins E, Bennett P, Kumar S. Umbilical venous flow rate in term fetuses: can variations in flow predict intrapartum compromise? Am J Obstet Gynecol. 2014 Jan;210(1):61.e1-8. doi: 10.1016/j.ajog.2013.08.042. Epub 2013 Aug 30.

Prior T, Mullins E, Bennett P, Kumar S. The influence of parity on fetal haemodynamics and amniotic fluid volume at term. Ultrasound Obstet Gynecol. 2014 Feb 15. doi: 10.1002/uog.13332.

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Prior T, Mullins E, Bennett P, Kumar S. Prediction of fetal compromise in labor. Obstet Gynecol. 2014 Jun;123(6):1263-71. doi: 10.1097/AOG.0000000000000292.

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Prior T, Paramasivam G, Bennett P, Kumar S. Are babies that fail to reach their genetic growth potential at increased risk of intra-partum fetal compromise? (accepted - in press) Ultrasound Obstet Gynecol.

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A comparison of fetal Doppler indices between primiparous and multiparous women Oral presentation at ISUOG conference, Sydney, October 2013

Prediction of intra-partum fetal compromise in normal pregnancies: a composite risk score Oral presentation at ISUOG conference, Sydney, October 2013 (Best oral presentation)

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Blair Bell Meeting, London 2012

Accuracy of sonographically determined estimated fetal weight at term in a low risk population, ISUOG, Copenhagen 2012

Emergency caesarean section for fetal distress in labour is associated with smaller infants than spontaneous vaginal delivery, Copenhagen ISUOG 2012

Pre-labour fetal cerebro-umbilical ratio is predictive of intra-partum fetal distress, BMFMS 2012 Glasgow

Prediction of intra-partum fetal distress using pre-labour fetal cerebro-umbilical ratio, Blair Bell Meeting,
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Abstract

Obstetric practice aims to mitigate the potential adverse effects of intra-partum fetal compromise by identifying the compromised fetus and expediting delivery before permanent neurological damage ensues. The ubiquitous use of the cardio-tocograph as a method of intra-partum fetal surveillance has not resulted in a reduction in the incidence of cerebral palsy and has been held responsible for increasing rates of medical intervention in birth. As a result, its use is not recommended in low risk pregnancy. However, the classification of all pregnancies without antenatal complication as low risk may be inappropriate, given that a significant proportion of cases of fetal hypoxia occur within this cohort. A more individualised approach to risk stratification is therefore required. This thesis will report the development of a technique to risk stratify 'low risk' pregnancies prior to established labour.

In a prospective observational study, ultrasound assessment incorporating umbilical and middle cerebral artery Doppler, and evaluation of 1st trimester B-HCG and PAPP-A levels, were investigated to determine if these parameters were predictive of subsequent intra-partum fetal compromise and the need for emergency delivery. Ultrasound assessment was undertaken both at term prior to established labour (in 604 cases), and at 35 – 37 weeks gestation (in 125 cases). A single trained practitioner undertook all ultrasound assessments, and staff managing the labour were blinded to the ultrasound results. Cases were followed up within 72 hours of delivery and intra-partum and neonatal outcomes evaluated. Multiple parameters (umbilical artery PI, middle cerebral artery PI, the cerebro-umbilical ratio and umbilical venous flow) were combined to create a composite risk score to predict intra-partum fetal compromise. Finally, maternal hyper-oxygenation was investigated as a potential therapeutic tool to improve fetal haemodynamics.

Ultrasound assessment prior to active labour can identify fetuses at high and low risk of subsequent intra-partum compromise, even within a 'low risk' population. The cerebro-umbilical ratio may be the single most predictive parameter, with fetuses with the lowest ratios at significant increased risk of subsequent compromise in labour (RR 21.00, 95% CI 2.92 – 151.00). Maternal hyper-oxygenation did not influence the measured fetal Doppler parameters.

Ultrasound assessment may facilitate a more individualised approach to fetal assessment, allowing women to make better informed decisions regarding labour and delivery.

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Statement of candidate contribution

My supervisor Professor Sailesh Kumar and I generated the hypotheses within this thesis. I developed the study design with assistance from Professor Kumar. I undertook all the described ultrasound assessments, data collection, participant follow up, and data analysis.

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Chapter 1 - Introduction

This thesis reports research spanning the period January 2011 to January 2014. The time periods during which each individual study was undertaken are reported in the methods section of the relevant chapter.

Despite improved antenatal, intra-partum, and neonatal care, the incidence of cerebral palsy in term infants has not changed significantly over the last thirty years[1]. Whilst evidence suggests that the majority of cases of cerebral palsy have their aetiology in the antenatal period[2] [3], a significant proportion remain attributable to intra-partum events[4] [5]. Such cases are more likely to be preventable, with improved outcomes resulting from timely intervention during labour. Intra-partum events leading to cerebral palsy and other neurological sequelae are over represented in medico-legal malpractice cases[6], and often result in the award of a large quantum of financial compensation[7]. With the possibility of affected individuals requiring a lifetime of care, and the spiralling costs of medico-legal malpractice insurance, intra-partum fetal compromise continues to represent a significant financial burden to healthcare providers around the world. The psychological and emotional impact on both the affected individual and caregivers is enormous[8].

With this in mind, different methods of identifying fetal hypoxia during labour have evolved; all with the primary aim of expediting delivery before irreversible brain injury occurs. However, paradoxically, the use of intra-partum monitoring is associated with an increased incidence of operative delivery for presumed fetal compromise[9] without a reduction in the incidence of cerebral palsy.

Why some babies are more prone to intra-partum compromise is not entirely clear. Although there is some association with other pathology, such as fetal growth restriction[10, 11]as much as 63% of cases of intra-partum hypoxia occur in pregnancies with no antenatal risk factors[12]. Impaired placental transfer of oxygen and other substrates during labour is likely to be responsible for the “fetal distress” that develops as a consequence of regular uterine contractions, which can reduce uterine blood flow by as much as 60%[13].

The final common pathway of many conditions that result in fetal growth restriction is one of placental insufficiency[14]. Placental function may be evaluated by ultrasound[15]

assessment of fetal biometry[16, 17] , haemodynamics[18, 19] and amniotic fluid volume . An approximation of placental function may also be made indirectly, by measurement of various biomarkers in the maternal circulation such as pregnancy associated plasma protein A (PAPP-A)[20], Placental Growth Factor (PlGF)[21], Vascular Endothelial Growth Factor (VEGF)[21], and Insulin like Growth Factor (IGF)[22]. Several placental hormones in the maternal circulation are measured as part of first trimester screening for aneuploidies, and a low levels of PAPP-A have been strongly linked with subsequent abnormalities in fetal growth[23].

What is currently unknown is whether alterations in fetal haemodynamics, amniotic fluid volume, and placental hormone levels can identify evidence of placental dysfunction in an appropriately grown fetus, and be predictive of a subsequent diagnosis of fetal compromise in labour.

Intra-partum fetal hypoxia - A problem of global importance

Intra-partum hypoxia can lead to hypoxic ischaemic encephalopathy (HIE), cerebral palsy and stillbirth. Neonatal encephalopathy describes the immediate neurological sequelae of HIE which include altered consciousness level, neonatal seizures, and abnormalities on neurological examination[24] . Fortunately, hypoxic ischaemic encephalopathy is an infrequent occurrence, affecting around 1.5/1000 of live births[25] in developed countries. However, in affected cases the resulting neurological damage can have catastrophic effects for both the individual involved and their family. Even in developed countries, birth asphyxia remains the strongest and most consistent risk factor identified in children with cerebral palsy born at term[26].

Intra-partum stillbirth is rarer still, occurring in around 0.9/1000 of births in developed countries[27]. However, the incidence varies widely in less well resourced countries, being as high as 20-25/1000 births in some parts of Africa[27]. Even with modern obstetric practice, the risk of death on the day of birth is greater than any other single day up to the 92nd year of life[28]. Intra-partum stillbirth rates are strongly correlated with the availability of antenatal care, and of emergency caesarean delivery[27]. Every year, 904,000 neonatal deaths are attributed to intra-partum birth asphyxia[29], and following reductions in

childhood mortality of other causes, intra-partum events are becoming increasingly prominent[30]. Ninety nine percent of deaths attributable to intra-partum hypoxia occur in low-middle income countries[31], countries where 60 million births occur each year away from recognised health facilities, and often without a skilled birth attendant[32].

In the year 2000 the United Nations identified a group of development targets to be achieved by the year 2015. One of these "Millennium Development Goals" (MDG) was to reduce child mortality less than 5 years of age to 32 per 1000 live births, a reduction of two thirds[30]. Addressing intra-partum care in the developing world was a key component in achieving this target, as more deaths occur due to labour and delivery than HIV and Malaria combined[32].

Severe neurological disability is seen in approximately 25% of babies with HIE, and in addition to cerebral palsy may include epilepsy, sensory loss, and developmental delay[33] . The severity of HIE may be graded as mild, moderate or severe in the first few days of life using the Sarnat score. This scoring system incorporates parameters from both clinical assessment and the electroencephalogram (EEG)[34]. Whilst features of HIE may be apparent in the immediate neonatal period, in some cases the neurological sequelae may not be revealed until much later in life and may only be manifested by educational difficulties once the child reaches school age[35]. Outcomes for infants with mild encephalopathy are predominantly good, those with severe encephalopathy are almost invariably bad, whilst those with moderate encephalopathy represent a much more heterogeneous group[36]. Long term studies demonstrate that children with a history of HIE may develop neurodevelopmental deficits, including a reduction in IQ, even in the absence of major disability[37] .

Cerebral palsy, a diagnosis which itself encompasses a wide range of disability, may be attributed to HIE in cases where an umbilical artery pH of <7.0 was present at birth, there was moderate or severe neonatal encephalopathy and no other causative mechanism is identified[24] .

Despite the relatively infrequent occurrence of HIE in developed countries, the associated financial implications mean it still exerts a significant impact on healthcare services. In the United Kingdom, whilst Obstetrics and Gynaecology accounts for 20% of all claims made to

the NHS Litigation Authority (NHSLA), in monetary terms these claims amount to 49% of all compensation paid by the NHSLA, some £5.2 billion between 1995 and 2011[7]. The clinical negligence scheme for trusts (CNST), which provides malpractice indemnity for the NHS via the NHSLA, costs NHS hospitals almost £1 billion a year[38]. The Obstetric component of this sum in England alone is £452 million, 1/5th of the entire NHS maternity budget, and equivalent to £700 for each birth[39]. Identification of infants at risk of intra-partum compromise therefore remains a problem of global importance.

Placental development and establishment of the feto-placental circulation

The fetal component of the placenta develops from the outer layer of the blastocyst, the trophoblast. This attaches to the maternal component of the placenta, the decidua basalis, via the outer layer of trophoblastic cells, the cytotrophoblastic shell. Until the eighth week, chorionic villi, derived from the trophoblast, cover the entire chorionic sac, but as the sac develops, the chorionic villi associated with the decidua degenerate and form the villous chorion, the fetal part of the placenta. Stem villi arise from the villous chorion and pass into the inter-villous space. This area, formed by the fusing of multiple lacunae in the endometrium is filled with maternal blood. The interaction of the villous chorion and maternal blood in the inter-villous space enables transfer of nutrients and waste products between the maternal and fetal circulations.

Trophoblastic invasion of the decidua requires digestion of the extracellular matrix (ECM), a process mediated by a variety of proteases and gelatinases such as MMP-9[40] which are secreted by the invading trophoblast. Endovascular cytotrophoblast cells invade the spiral arteries leading to morphological changes in their structure and resulting in increased perfusion of the placental bed. The precise mechanism through which the spiral arterioles are uncoiled, and a low resistance circulation established, are yet to be determined, but vasodilating mediators such as Nitric Oxide and Carbon Monoxide have both been implicated in this process[41, 42]

As well as enabling transfer of nutrients/waste products between the maternal and fetal circulations, the developing placenta also performs a number of crucial endocrine functions. Production of Human Chorionic Gonadotrophin (HCG) by the trophectoderm supports the corpus luteum, and in doing so maintains an adequate progesterone level for the

continuation of the pregnancy[43]. Pregnancy associated plasma protein A (PAPP-A) is also synthesised by the placenta and acts as a regulator of fetal growth via its interaction with Insulin-like growth factor binding protein 4 (IGFBP4), a potent inhibitor of Insulin-like growth factor (IGF)[44]. Produced by the placental trophoblast, Placental Growth Factor (PlGF) is an angiogenic growth factor which plays a role in both vasculogenesis and angiogenesis in the developing fetus through its action on endothelial cell proliferation[21].

Placental development and function in fetal growth restriction and pre-eclampsia

Placental dysfunction and the conditions associated with it may be precipitated by sub-optimal placental development in early pregnancy[45]. Re-modelling of the maternal spiral arteries, a process at least in part stimulated by trophoblastic invasion of the decidua, results in a reduced resistance to flow in the utero-placental circulation[46] and consequently increased perfusion. There is evidence this process is defective in pregnancies complicated by fetal growth restriction[47], leading to sub-optimal trophoblastic invasion and the maintenance of a high resistance placental circulation[48]. Defective trophoblastic invasion is also a feature of pre-eclampsia, and is associated with a failure of up-regulation of MMP-9[49]. Animal studies demonstrate that MMP-9 deficient mice display placental features consistent with pre-eclampsia as well as producing growth restricted offspring[50]. Deficiencies in the conversion of trophoblastic cell adhesion molecules to an endothelial cell phenotype, critical for vasculogenesis within the developing placenta, are also present in pre-eclampsia[51]. The failure of these processes may result in limited endovascular invasion[49].

Immunological abnormalities have also been implicated in poor placentation. Trophoblast expresses HLA-G, a major histocompatibility complex with a low degree of polymorphism[52], and in doing so may be protected from the cytotoxic actions of maternal NK cells within the decidua[53]. Expression of HLA-G is reduced in pre-eclampsia, potentially leaving the trophoblast vulnerable to attack[49]. Other complications of pregnancy, including in-utero death and fetal distress in labour also have a placental aetiology[54].

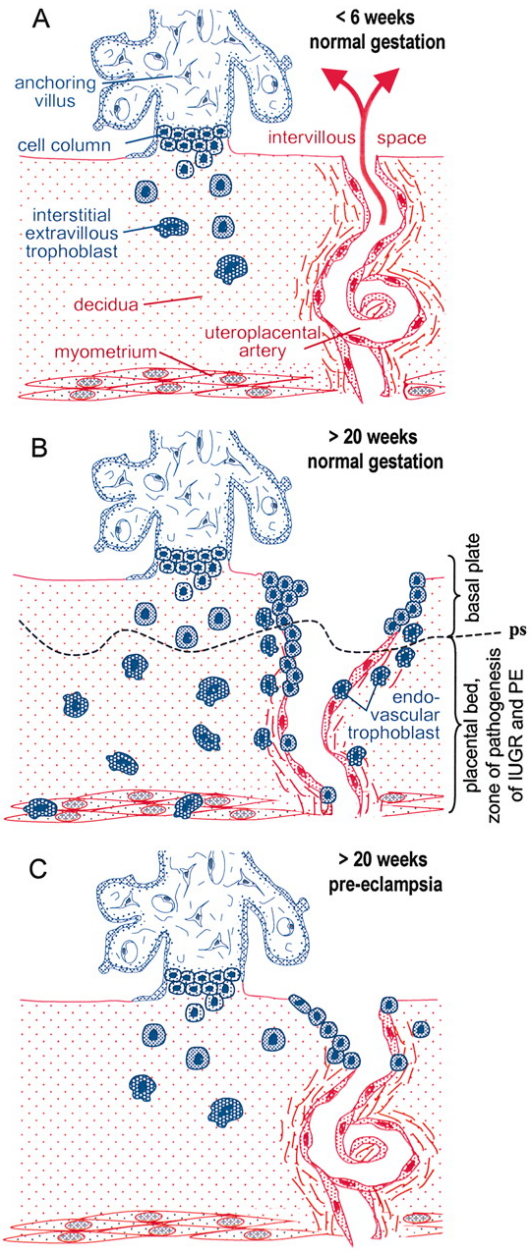


Figure 1 Spiral artery changes in normal pregnancy and pre-eclampsia. Taken from *Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod. 2003 Jul;69(1):1-7. Epub 2003 Mar 5*[46].

Fetal growth restriction is also associated with abnormalities in placental amino acid[55], glucose, and fatty acid metabolism[48]. Histo-pathological abnormalities, such as an increase in the proportion of syncytial knots (aggregates of syncytiotrophoblastic nuclei on the surface of the terminal villi[56]), have been reported in placentae of growth restricted babies. Other abnormalities include abnormal fibrin deposition, which may impede blood flow to the superficial villi. The incidence of several placental abnormalities known to be associated with fetal growth restriction and placental dysfunction, also correlate with the severity of umbilical artery Doppler flow velocity waveform abnormalities[57], with an increase in syncytial knots, and placental giant cells evident in cases with absent/reversed end diastolic flow[58] in the umbilical artery. Other studies have observed a significant relationship between the presence of villous infarction and thrombi formation in the placenta, and Doppler abnormalities in the umbilical and uterine arteries[59]. Placental weight is also significantly reduced in small for gestational age fetuses[60]. Interestingly, appropriately grown fetuses that become distressed during labour and require emergency delivery also have reduced placental weights compared to those fetuses that tolerate labour well[61, 62].

How does labour affect the feto-placental unit

Changes in the intra-uterine environment that occur during labour can precipitate fetal compromise. Human birth is hampered by the dimensions of the female pelvis, which has its largest diameter in the transverse plane at the pelvic inlet, and in the anterior-posterior plane at the pelvic outlet. The shape of the maternal pelvis, coupled with the relatively large term fetal cranium, makes it necessary for the fetus to rotate as it descends through the birth canal in order to traverse both the pelvic inlet and outlet. The process of parturition in humans is thus much more complex than in closely related mammals such as the Chimpanzee and Gorilla who possess a more capacious pelvis. The challenges of childbirth in humans are a likely consequence of the evolutionary development of bipedalism and a large brain size[63].

Intra-partum fetal hypoxia may be precipitated by a sudden interruption of placental perfusion, either on the maternal or fetal side, following maternal hypotension, placental abruption, or umbilical cord prolapse. However, more frequently there is a gradual

deterioration in the fetal condition during labour reflecting a steady deterioration in the ability of the placenta to support the fetus as labour progresses.

It is during labour that the feto-placental relationship is tested to the greatest degree. In association with contractions, intra-uterine pressures can increase to more than 150mmHg, and uterine artery blood flow velocities are reduced by as much as 60%[13]. Other studies have suggested that intra-uterine pressures of just 35mmHg are sufficient to decrease uterine artery end diastolic velocities to zero[64], resulting in reduced placental perfusion and precipitating fetal compromise. The fetus responds to uterine contractions with acute cerebral re-distribution, evidenced by a raised umbilical artery pulsatility index and a reduced middle cerebral artery pulsatility index[65]. This centralisation of blood flow is a well-documented response to placental insufficiency observed in growth restricted fetuses in the antenatal period[66]. These changes are associated with an increased incidence of intra-partum fetal compromise[67]. An association between placental insufficiency and the development of intra-partum fetal compromise is therefore already established.

Fetuses exposed to increased levels of uterine activity during labour, are more likely to be acidotic at delivery[68]. Furthermore, in multiparous women, whose pregnancies are rarely complicated by intra-partum fetal compromise, intra-uterine pressures during labour are significantly lower than those of nulliparous women[69]. The potentially adverse impact of uterine contractions on the fetus is evident in that abnormal fetal heart rate patterns occur more frequently in association with uterine contractions than in the presence of a relaxed uterus.

Initially the feto-placental circulation was suggested to be relatively resistant to the effects of uterine contractions[70]. However, more recently, alterations in the umbilical artery resistance of fetuses with evidence of placental dysfunction, have been observed as a consequence of uterine activity[71, 72]. Alterations in cerebral blood flow, with the acute development of a brain sparing circulation, have also been observed during contractions, even in fetuses where such brain sparing is absent under basal conditions[73].

The reduction in utero-placental blood flow associated with contractions may therefore precipitate fetal compromise.

How does Hypoxia lead to neuronal damage?

Energy production via oxidative phosphorylation is the process by which respiring organisms re-form adenosine triphosphate (ATP), an energy rich molecule that can then be used to power metabolic processes. Oxygen plays a critical role in this process, by acting as an electron acceptor in a series of reduction-oxidation reactions. Without sufficient oxygen supply, oxidative metabolism cannot be maintained, and the cell will instead resort to anaerobic metabolism. In this process, pyruvate, derived from glycolysis, is reduced to Lactic acid, yielding ATP molecules.

Under hypoxic conditions, several processes contribute to neuronal damage. Hypoxia is associated with a significant rise in intra-cellular calcium concentration[(74)], which in turn leads to the release of neurotoxic excitatory amino acids such as Glutamate and Aspartate[(75)]. These excitatory amino acids bind to receptors and stimulate a process that results in the release of apoptotic proteins and subsequent cell death[(76)]. Cerebral hypoxia-ischaemia leads to the production of Oxygen free radicals[(77)], which disrupt cellular membranes and result in cell damage[(78)]. The cellular influx of calcium stimulated by Glutamate, activates Nitric Oxide (NO) synthase, and results in the production of highly potent radicals, which in turn can precipitate cell damage[(77)]. These insults result in neuronal death by both necrotic and apoptotic pathways.

The brain is particularly vulnerable to hypoxic conditions due to its high energy requirements and limited energy reserves[(79)]. Under acute hypoxic conditions neuronal energy metabolism falters after only a few minutes[(80)]. Evidence suggests that compared with the adult brain, the neonatal brain may have further increased vulnerability to hypoxia owing to a greater susceptibility to oxidative stress[(81)].

Pathological brain lesions associated with hypoxia-ischaemia

Hypoxic-ischaemic brain lesions may take several forms.

Selective neuronal damage – This can occur after hypoxia lasting just 10 minutes[82], and predominantly affects neurones of the cerebral cortex. Border areas at the periphery of the territories of major arteries are affected worst, as well as the cerebellum, hippocampus, and anterior horn cells of the spinal cord[83].

Parasagittal neuronal injury – This predominantly affects the parietal and occipital regions and occurs following insufficient perfusion of the regions bordering the territories of major cerebral arteries.

Periventricular leucomalacia – damage to the white matter adjacent to the lateral ventricles[83]. Occurs much less frequently in fetuses of later gestation (>32 weeks gestation). Necrotic insults lead to swelling and rupture of axons, and necrosis of oligodendrocytes[84].

Intra/periventricular haemorrhage - also occurs more frequently in pre-term fetuses. These lesions originate in the vascular bed of the germinal matrix, an area that largely disappears by full gestation[85].

Focal/multifocal brain injury – affects the territories of the main cerebral arteries, and consists of an infarct involving all cell types[84].

The impact of such neuronal damage is significant. As a consequence, the identification of fetal compromise, enabling timely intervention before permanent neurological damage occurs has been the target of research for almost 200 years.

The evolution of fetal monitoring

In 1822 the French physician, Kergaradec, published a paper reporting the auscultation of the fetal heart beat to confirm fetal wellbeing [(86)]. Only a year later, a manuscript documenting the use of fetal heart auscultation during labour to guide decision making was published[(87)]. In 1838, Schwarz proposed what would later be known as intermittent fetal monitoring during labour, suggesting that the fetal heart be auscultated as often as possible during parturition[(88)]. However, it wasn't until 1903 that Seitz published a paper delineating different types of fetal heart rate decelerations, reporting that some decelerations could be viewed as a warning, and used to expedite delivery and improve prognosis for the fetus[(89)].

In 1957, Dr Orvan Hess and Dr Edward Hon first described a technique for the continuous recording of fetal electrical cardiac signals.[(90)]. Initially monitoring was invasive, with electrodes attached directly to the fetal presenting part, but in 1964, ultrasonic auscultation of the fetal heart was first reported[(91)] and from 1960 onwards electronic monitoring of the fetal heart rate became routine practice in developed countries[(92)]. It was hoped that the introduction of this technique to clinical practice would reduce the incidence of cerebral palsy. However, whilst the use of electronic fetal heart rate monitoring does result in a reduction in the incidence of neonatal seizures, no such effect has been demonstrated on the incidence of cerebral palsy[(93)]. In conjunction with this somewhat disappointing outcome, electronic fetal heart rate monitoring has been associated with an increased incidence of operative delivery for presumed fetal compromise[(9)]. The poor specificity of fetal heart rate monitoring for true fetal compromise is well documented, with a false positive rate of as much as 99.8% in some studies[(94)].

Interpretation of fetal heart rate patterns is complicated by significant intra and inter observer variability[(95, 96)]. In an effort to address this, FIGO[(97)] (International Federation of Gynaecology and Obstetrics), the American Congress of Obstetricians and Gynecologists[(98)], and the National Institute for Health and Clinical Excellence in the UK[(99)], have all published guidelines to standardise interpretation of fetal heart rate patterns. Use of such guidelines has been reported to result in a reduction in the incidence of hypoxic-ischaemic encephalopathy[(100)]. However, even amongst these guidelines there is disparity in the definition of different types of decelerations and of the classification of suspicious and pathological patterns[(101)]. Significantly, despite the widespread circulation of these guidelines, fetal heart rate pattern misinterpretation and subsequent suboptimal obstetric

management remain by far the leading cause of medico-legal litigation claims in Obstetrics,[102, 103].

To mitigate high inter-observer variability, computerised analysis of fetal heart rate patterns was developed over 20 years ago[104]. These systems use software packages that record and analyse fetal heart rate tracings according to a set of pre-programmed characteristics, providing audio and visual alerts to the user. These systems are reported to have greater predictive value for fetal acidosis at delivery[105], and perform better than Obstetricians in identifying the compromised fetus[106]. However, despite computerised analysis showing some promise[107], there is a paucity of data from large randomised trials demonstrating improved neonatal outcomes. This information is essential to support the use of these systems in clinical practice. One such study is currently in progress[108].

Despite a large retrospective population study recently reporting an association between the temporal increase in the use of continuous fetal monitoring in the United States with a reduction in neonatal mortality[109], the value of continuous fetal monitoring to identify intra-partum hypoxia and improve neonatal outcomes remains the subjective of considerable debate[110]. However, the use of continuous fetal monitoring does result in a reduction in neonatal seizures[111], and it should be noted that the majority of trials evaluating its use included in systematic reviews such as those of Alfirevic et al[112], and in the preparation of NICE guidance, were conducted some time ago, potentially limiting their ability to be representative of contemporary practice.

Cardio-tocograph analysis in clinical practice

In the UK, caregivers are expected to adhere to the NICE guidelines for cardio-tocograph (CTG) interpretation.

Table 3 Categorisation of fetal heart rate traces

Category	Definition
Normal	A CTG where all four features fall into the reassuring category.
Suspicious	A CTG whose features fall into one of the non-reassuring categories and the remainder of the features are reassuring.
Pathological	A CTG whose features fall into two or more non-reassuring categories or one or more abnormal categories.

Table 4 Categorisation of fetal heart rate (FHR) features

Feature	Baseline (bpm)	Variability (bpm)	Decelerations	Accelerations
Reassuring	110–160	≥ 5	None	Present
Non-reassuring	100–109 161–180	< 5 for >40 to <90 minutes	Early deceleration Variable deceleration Single prolonged deceleration up to 3 minutes	*The absence of accelerations with an otherwise normal CTG are of uncertain significance*
Abnormal	<100 >180 Sinusoidal pattern ≥ 10 minutes	<5 for ≥ 90 minutes	Atypical variable decelerations Late decelerations Single prolonged Single prolonged deceleration >3 minutes	

Figure 2 NICE guidelines for CTG interpretation

Interpretation of the CTG is commonly undertaken by considering its five constituent parts individually, before combining these to give an overall assessment. The basal fetal heart rate is normally between 110 and 160 beats per minute. A baseline bradycardia (100-110 beats per minute) or a baseline tachycardia (160-180 beats per minute), in the absence of any other abnormalities, does not suggest fetal acidosis[113]. A change in baseline rate may be more ominous, with a rising baseline indicative of utero-placental insufficiency, and a sudden prolonged bradycardia strongly associated with fetal acidosis.

Baseline variability describes the variation of the fetal heart rate above and below the baseline rate. Variability of 5-25 beats per minute represents the interplay of the sympathetic and para-sympathetic nervous systems. The presence of fetal heart rate variability therefore implies a functioning central nervous system and is a reassuring feature[114].

Accelerations are periods of elevation of the fetal heart rate above the baseline rate of more than 15 beats per minute for more than 15 seconds. Accelerations often occur in association with fetal movement, and are therefore suggestive of an intact somatic nervous system. The presence of accelerations appears to rule out fetal acidosis[113].

Decelerations are periods of reduction of the fetal heart rate below the baseline of more than 15 beats per minute lasting greater than 15 seconds. Decelerations may be described as “early”, “variable” and “late” in reference to their association with uterine contractions. Early decelerations occur as a mirror image of uterine contractions. They are associated with head compression and are often seen in the late first stage and second stage of labour. Variable decelerations vary in shape and timing relative to uterine contractions. They may be described as “typical”, lasting less than 60 seconds, or “atypical”, lasting longer than 60 seconds. They are often associated with cord compression, although persistent atypical variable decelerations may be ominous. Late decelerations have their peak after the peak of the uterine contraction and are suggestive of utero-placental insufficiency[114].

Analysis of the CTG also requires assessment of uterine activity. Uterine activity of more than 4-5 contractions per 10 minutes is termed tachysystole, or if associated with pharmacological augmentation, hyperstimulation.

Fetal Blood Sampling

To compensate for its poor specificity, intra-partum fetal heart rate monitoring is frequently augmented with the use of fetal blood sampling (FBS). This technique, which has been used since the 1960's[115], involves the acquisition of a small sample of blood from the fetal scalp under direct vision. The blood sample may then be immediately analysed, and the acid-base status of the fetus assessed. Decisions on further management are then based on blood pH levels, which have a greater correlation with neonatal condition than either pO2 or pCO2[116]. Fetal blood sampling has been demonstrated to have a greater specificity for low Apgar score at 1 minute than fetal heart rate monitoring[117]. However, despite these benefits, the use of FBS has not been shown to improve neonatal outcomes[117], or to reduce the incidence of caesarean delivery for presumed fetal compromise[118]. The use of FBS also varies considerably between different maternity units, and even between individual Obstetricians[119]. Limitations of FBS include its invasive nature, and the possible difficulties of acquiring adequate samples during labour. The procedure generally requires cervical dilatation of 3cm or more, may be intolerable for women without sufficient analgesia, and can be hampered by contamination of the blood specimen with air or amniotic fluid. As a result of these limitations, insufficient samples are obtained in as many as 20% of cases[120]. Even if optimal samples are obtained, they provide information on the fetal condition only at the time of sampling, meaning repeated sampling may be required. Importantly, despite a normal FBS sample (pH>7.30), fetuses with abnormal heart rate patterns are still at increased risk of a low Apgar score at delivery compared to those with normal heart rate patterns[121].

Assessment of fetal lactate levels, via intra-partum fetal blood sampling, has also been suggested as a method to evaluate fetal wellbeing in the presence of a non-reassuring fetal heart rate pattern. Lactate has been reported to be more predictive of neonatal encephalopathy and low Apgar scores than pH alone[122]. Despite this, two randomised controlled trials comparing the use of lactate and pH failed to demonstrate an improvement in neonatal outcomes, or a change in operative delivery rates,[123, 124]. Whilst reports in 2005[125] and 2008[126]did not demonstrate a correlation between lactate levels and Apgar scores at delivery, an observational study published in 2011 suggested lactate levels do have a greater correlation with metabolic acidosis at delivery than either scalp pH or base deficit[127]. A systematic review in 2010 concluded that while current evidence suggested the efficacy of fetal lactate was at least equivalent to that of pH for the identification of the

compromised fetus, further studies designed to evaluate diagnostic accuracy were required[120].

Other methods of intra-partum fetal monitoring

As a result of the inadequacies of continuous fetal heart rate monitoring, numerous other techniques have been developed to facilitate the identification of the compromised fetus during labour. These include assessment of the fetal electrocardiogram (ECG), and fetal pulse oximetry.

Fetal Electrocardiogram

The fetal ECG has the same composition as that of an adult, with the P-wave, QRS complex and T-wave representing atrial contraction, ventricular contraction and ventricular repolarisation respectively. Changes in both the ST segment and the P-R and R-R intervals have shown the greatest promise for intra-partum fetal assessment. In an ovine model, both ST segment elevation[128] and shortening of the P-R interval [129] were observed in response to fetal hypoxia. A randomised trial evaluating the use of ST segment analysis (STAN©) in addition to CTG was conducted in 1993. Whilst the addition of ST segment analysis did result in a significant reduction in the incidence of operative delivery for presumed fetal compromise, this reduction was amongst cases with CTG recordings classified as normal or suspicious. ST segment analysis had no effect on the incidence of operative delivery in cases with a pathological fetal heart rate pattern[130]. A recent meta-analysis suggested ST segment analysis does not result in a reduction in the incidence of operative delivery for presumed fetal compromise, or of fetal acidosis at the time of delivery, but does result in a reduction in the number of FBS procedures performed[131]. The limited impact of STAN© on neonatal outcomes and operative delivery rates may be attributable to a failure to follow STAN© guidelines. Cases of neonatal encephalopathy and acidosis at delivery, where STAN© was used during intra-partum care, are frequently associated with a deviation of clinical practice from STAN© guidelines,[132, 133]. However, it is also concerning that in some cases, fetuses born with significant acidosis at delivery experience no ST segment changes during labour[134-136].

Fetal ECG monitoring is less invasive than fetal blood sampling, but does require attachment of an electrode to the fetal scalp. As a result this technique still demands a degree of cervical dilatation, and cannot be undertaken when amniotic membranes are intact. Other limitations include the short time period (20 minutes) in which delivery should be achieved following an ST event, poor signal quality, and the difficulty of interpreting CTG recordings in accordance with STAN guidelines[136].

Fetal pulse oximetry

Measurement of fetal blood oxygen saturation using fetal pulse oximetry was first described in 1989[137], with reports of continuous intra-partum monitoring of fetal oxygen saturation following shortly after[138]. Assessment of oxygen saturation is widely used in adult medicine, but despite some promising results, the use of fetal pulse oximetry has not been established to a similar extent. The proposed benefits of fetal pulse oximetry include the continuous assessment of fetal wellbeing, with greater specificity than CTG as well as being a less invasive intervention than fetal blood sampling. Pulse oximetry relies on the different absorption spectra of oxygenated and deoxygenated haemoglobin. Light in both the red and infrared range of the electromagnetic spectrum are emitted by light emitting diodes, and the relative absorption of both used to determine the oxy/deoxyhaemoglobin content of the blood[139]. In contrast to many pulse oximeters, fetal pulse oximeters function via the reflectance technique, meaning both the light emitter and photo-detector may be positioned in the same plane[140]. Reports suggest that during labour the normal fetal oxygen saturation lies between 58% and 68%[141], with a reduction to <20% occurring during acute cord compression[142]. A fetal oxygen saturation of <30% has been associated with fetal acidosis if persistent for several minutes,[143, 144] and measurements at delivery are reported to correlate well with umbilical vein oxygenation and cord blood pH[145]. However, despite these promising results, the evidence for clinical benefit remains equivocal. Randomised controlled trials in both 2000 and 2004, did suggest that the use of fetal pulse oximetry lead to a reduction in the incidence of operative delivery for presumed fetal compromise without an increase in adverse neonatal outcomes[146, 147]. However, these results were not replicated in further trials conducted in 2006[148, 149]. Several factors are reported to influence the performance of fetal pulse oximetry, with fetal hair, caput succedaneum and sensor position affecting readings taken from the fetal scalp[150].

Furthermore, a Cochrane review published in 2007 concluded that whilst the available evidence offered limited support for the use fetal pulse oximetry, this technology did not lead to a reduction in caesarean section rates[151].

Identifying the fetus at risk of compromise during labour

As intra-partum CTG monitoring is associated with a high false positive rate, a selective approach to its use is prudent. Current guidance in the UK does not recommend the use of this monitoring tool in pregnancies classified as low risk[152]. The term "low risk" is used to describe those pregnancies where no adverse risk factors (pre-eclampsia, fetal growth restriction, advanced maternal age etc.) have been identified in the antenatal period. However, identifying a pregnancy as low risk for intra-partum compromise remains challenging, as evidence suggests that the majority of cases of fetal hypoxia occur in pregnancies without identified antenatal complications[12]. Better identification of which antenatally low risk pregnancies, are at risk of developing fetal compromise in labour, would enable a more targeted approach to intra-partum care, exposing only those pregnancies at risk of fetal compromise to continuous CTG monitoring, and its associated increased incidence of operative delivery. With this aim in mind, various techniques have been reported.

Fetal biophysical profile

The fetal biophysical profile was developed as a means of fetal assessment in the 1980's, combining assessments of fetal breathing movements, fetal movements, and fetal tone, with assessment of amniotic fluid volume and the CTG[153]. Fetal movements have been considered a marker of fetal wellbeing for centuries, with authors as early as 1545 observing that an absence of fetal movements was indicative of intrauterine death[154]. A relationship between fetal breathing movements and fetal compromise was initially proposed in 1937. Snyder and Rosenfeld observed the cessation of fetal breathing movements in rabbits following a reduction in the concentration of maternal inspired Oxygen[155]. Similar observations were subsequently reported in sheep[156]. An association between reduced breathing movements in human fetuses and subsequent fetal compromise in labour was

published in 1979[157]. In 1980 Manning suggested that combining multiple markers of fetal wellbeing resulted in a more accurate method of antepartum fetal evaluation than any marker alone[153].

Several studies in the early 1980's suggested that the biophysical profile could be used to identify fetuses at risk of adverse perinatal outcome,[158, 159]. However, the biophysical profile was criticised for being labour intensive. This led to the development of the modified biophysical profile, which included assessment of the CTG and amniotic fluid volume only[160]. The rationale being that the CTG identifies acute fetal compromise, whilst the amniotic fluid volume allows assessment of longer term placental function. The largest observational series evaluating use of the modified biophysical profile for fetal monitoring demonstrated that its use could reduce the incidence of fetal death in a high risk cohort. However, this promising finding was mitigated by a high false positive rate of 60%[161]. Assessment of the biophysical profile in labour has also been used to predict intra-partum outcomes, with a biophysical profile score of six or less suggesting a significantly increased risk of caesarean delivery[162]. However, more recently a Cochrane review in 2008 suggested there was insufficient evidence to support the use of the fetal biophysical profile for fetal assessment in high risk pregnancy. This meta-analysis observed that in cases where the biophysical profile was used for monitoring, there was an increased incidence of both induction of labour and caesarean delivery[163].

Ultrasound monitoring of fetal wellbeing

Medical ultrasound devices use frequencies from 2-18MHz, with a higher frequency offering greater resolution but at the expense of penetration. Ultrasound waves, generated by piezoelectric crystals within the transducer, are reflected in varying degrees depending on the density of tissue. The disparate reflections are received by the transducer and interpreted by computer software to create a real time image.

Safety of ultrasound in pregnancy

Ultrasound has now been used as the principle imaging modality in pregnancy for over 30 years. Despite its widespread use in industrialised nations, there have been no large scale randomised controlled trials performed to investigate the effect of antenatal ultrasound on humans[164]. Reassuringly, systematic reviews of the available evidence have failed to identify any consistent deleterious effects of antenatal ultrasound[164, 165]. However, as this imaging modality utilises sound waves carrying energy, it is necessary that its possible effects be considered. When evaluating the safety of ultrasound, the implications of cavitation and heating have received the greatest attention.

Tissue heating

The degree to which biological tissue is heated by ultrasound waves depends not only on the energy content of the ultrasound, but also on the tissue composition and the rate of heat dissipation. Consequently, solid tissues and those with poor blood supply are the most vulnerable to heating effects[166]. Tissue heating may lead to direct tissue damage, but hyperthermia is also a recognised teratogen[19]. Accordingly, tissue heating during ultrasound assessment is monitored using the Thermal Index (TI). This measure, implemented in the early 1990's in response to increasing power outputs from ultrasound machines, describes the potential for temperature increases along the ultrasound beam[167]. There are three thermal indices, each being appropriate to the imaging of different tissues, Thermal index soft tissue (TIS), Thermal index - Bone at focus (TIB) and Thermal index - bone at surface (TIC)[168]. Maintenance of a TI ≤1 is recommended during ultrasound assessments with exposure times kept to a minimum and always < 60 minutes[169]).

Cavitation

Cavitation describes the effect of ultrasound waves on gas bubbles present at fluid-gaseous interfaces. Ultrasound waves may lead to two forms of cavitation, non-inertial cavitation, which describes oscillation of these gas bubbles, and inertial cavitation, which describes the growth of gas bubbles, which may then suddenly collapse releasing a large amount of heat, and causing direct damage to local tissues[170]. Cavitation appears to be of limited concern in human fetuses, due to the lack of fluid-gas interfaces for bubbles to form on[171]. The potential for cavitation is measured using the mechanical index (MI), which along with the TI is displayed on the ultrasound machine, giving the user responsibility to monitor these indices.

Despite concerns regarding both heating and cavitation, there is minimal evidence to support a detrimental effect of ultrasound on the fetus. Even in animal studies, using exposure levels far greater than those ever used clinically in humans, observed impacts on growth and haematological parameters appeared transient, with effects negligible by 3 months of age[172]. Studies in humans have also suggested a possible influence of ultrasound on fetal growth, with a higher incidence of low birthweight observed in fetuses exposed to multiple ultrasound examinations[173]. However, these effects are no longer evident by 1 year of age, and remained absent for the duration of follow up in the study, up to 8 years of age[174]. Studies such as this have led the authors of the most recent systematic review to conclude "ultrasonography in pregnancy is apparently not associated with important adverse maternal, perinatal or childhood effects"[164]. However given the potential for tissue damage when exposed to any energy source, the ALARA principle (as low as reasonably achievable)[175] remains applicable to the use of ultrasound in pregnancy.

Potential markers of fetal wellbeing include fetal weight, amniotic fluid volume, and assessment of blood flow velocity waveforms in various maternal and fetal vessels using Doppler ultrasound.

Fetal weight

Various formulae exist to estimate fetal weight from biometric measurements. Hadlock's formula, comprising bi-parietal diameter, head circumference, abdominal circumference, and femur length[176], is amongst the most commonly used in clinical practice. Currently, estimation of fetal weight is predominantly used to identify the pathologically small, growth restricted fetus, as well as those with potential macrosomia. Whilst birth weight is strongly linked to neonatal outcomes[177] for babies delivering preterm or those that are growth restricted, there is a paucity of data evaluating the impact of fetal size on neonatal outcomes amongst appropriately grown term fetuses.

Fetal growth restriction is associated with an increased risk of intra-partum fetal compromise and emergency delivery. In 1992, Weiss et al observed that growth restricted fetuses with severe abnormalities in umbilical artery flow (absent or reversed end diastolic flow), when allowed to labour, were delivered almost exclusively by caesarean section, usually due to the development of fetal compromise during labour [178]. Further studies have revealed that growth restricted fetuses, even without evidence of advanced placental dysfunction, are at increased risk of developing fetal compromise during labour[179]. Furthermore, it has also been reported that fetuses that fail to meet their growth potential, although >10th centile in birth weight, are more likely to develop CTG abnormalities in labour and require operative delivery[180]. Even amongst appropriately grown fetuses, mean birth weights and gestation matched birth weight centiles are significantly lower in fetuses developing signs of compromise during labour and requiring emergency delivery[181].

However, the use of fetal weight as a predictor of subsequent intra-partum fetal compromise is limited by the inherent inaccuracies associated with its estimation prior to birth. Whilst in large case series ultrasound derived estimated fetal weights have a high degree of correlation with birth weight[182], it is acknowledged that existing formulas used to calculate fetal weight are hindered by the possibility of large random errors. Furthermore, 95% confidence intervals for estimated fetal weight are frequently greater than 10% of birth weight[183].

Doppler ultrasound

The Doppler effect, named after the Austrian physicist who first described it in 1842, describes the change in frequency between a transmitted electromagnetic wave and its reflection, produced by the relative motion of its target.

The umbilical artery was the first fetal vessel to be imaged using Doppler ultrasound. In 1977, Fitzgerald and Drumm reported the use of a novel non-invasive technique to image the umbilical vein and umbilical artery[184]. In 1984, Schulman et al observed that fetuses that were small for gestational age had significantly higher umbilical artery systolic/diastolic ratios (S/D ratio), a marker of resistance to flow considered angle independent, and postulated a clinical application for the technique in antenatal care.

Doppler parameters

Several measures, derived from a flow velocity waveform, may be used to describe the waveform in a quantitative fashion, allowing objective comparison.

Pulsatility Index (PI) is a measure of the variance of blood flow velocity within the vessel throughout the cardiac cycle.

$$\text{Pulsatility Index} = \frac{\text{Peak systolic flow velocity} - \text{Trough diastolic flow velocity}}{\text{Mean blood flow velocity}}$$

The ***systolic/diastolic ratio*** (s/d ratio) is a measure of the resistance to flow within a vessel.

$$\text{S/D ratio} = \frac{\text{Peak systolic flow velocity}}{\text{Trough diastolic flow velocity}}$$

The ***Resistance index*** (RI) is also used to measure resistance to flow within a vessel.

$$\text{Resistance Index} = \frac{\text{Peak systolic flow velocity} - \text{Trough diastolic flow velocity}}{\text{Peak systolic flow velocity}}$$

Vmax describes the peak blood flow velocity recorded during the cardiac cycle.

Tamax or time averaged maximum velocity is a measure of the average blood flow velocity across the cardiac cycle.

End diastolic flow (EDF) describes the trough flow velocity at the end of diastole

Umbilical artery

Pulsed wave Doppler recordings form the umbilical artery have a “sawtooth” appearance, with peak velocities occurring during systole, and trough velocities occurring during diastole.

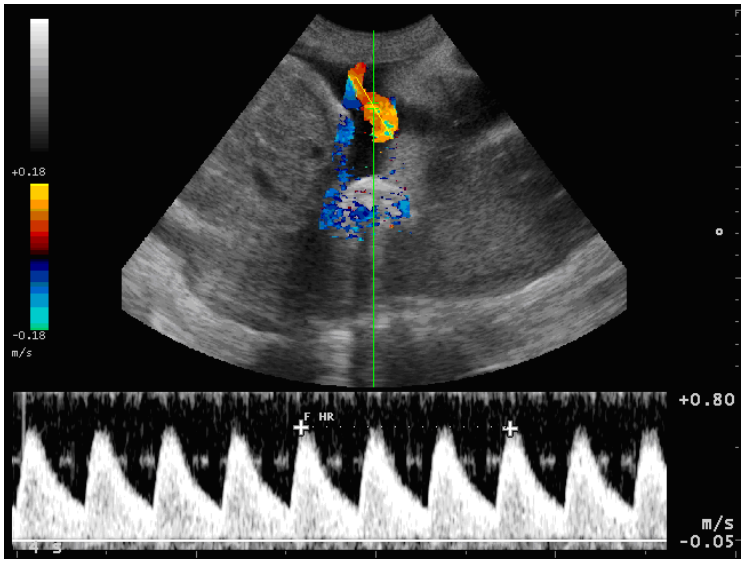


Figure 3 Umbilical artery flow velocity waveform acquisition.

In normal pregnancy, umbilical artery resistance declines gradually with advancing gestation[185], reflecting a reduction in resistance to flow within the placenta.

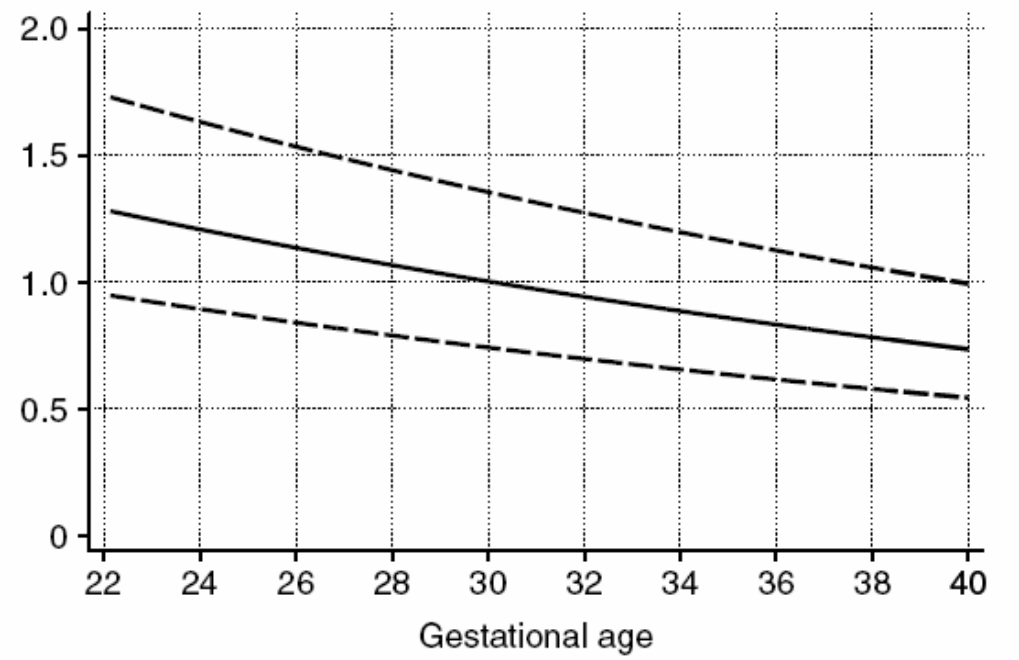


Figure 4 Umbilical artery PI according to gestation. Taken from : ***Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenat Diagn. 2007 Dec;27(13):1251-7.*** [185]

Changes in umbilical artery resistance are strongly linked with fetal growth restriction secondary to placental dysfunction[186]. A reduction in the number of placental arteries in the tertiary stem villi of the placenta is evident in these cases[187]. With regards to fetal growth restriction, the progression from normal to increased resistance flow, to absent and eventually reversed end diastolic flow in the umbilical artery is now well established[188, 189].

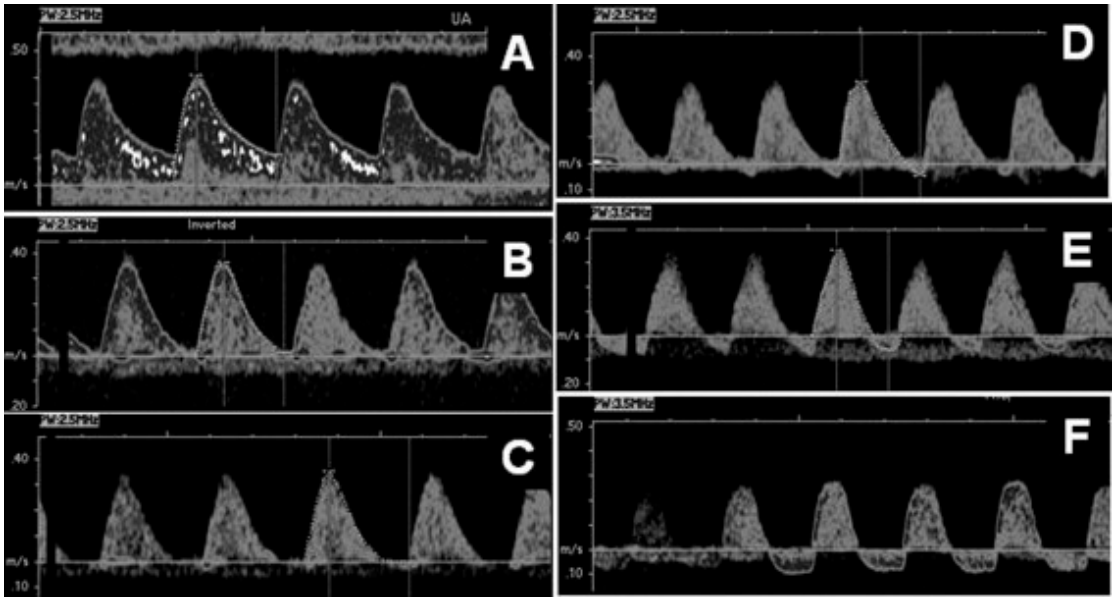


Figure 5 Progressive changes in Umbilical artery flow velocity waveform in fetal growth restriction. Taken from *"Miller J, Turan S, Baschat AA. Fetal growth restriction. Semin Perinatol. 2008 Aug;32(4):274-80. doi: 10.1053/j.semperi.2008.04.010.*[(189)]

As a consequence of these progressive changes, umbilical artery Doppler has been suggested as a surrogate marker of placental function[(190)], and is now established as a screening test to distinguish true fetal growth restriction secondary to placental dysfunction, in the context of a small for gestational age fetus.

Uterine contractions, despite being associated with a marked reduction in uterine artery flow velocities[(64)], are considered to have minimal effect on the umbilical artery vasculature. Both Fleischer et al, and Brar et al reported no variation in umbilical artery resistance measured before, during, or after contractions,[(64, 70)]. However, Li et al recorded umbilical artery PI in cohorts of fetuses with both a positive and negative response to an Oxytocin challenge test. They observed that during contractions fetuses felt to be imminently compromised (suggested by a positive Oxytocin challenge test) had a significantly raised umbilical artery PI compared to those with a negative Oxytocin challenge test, a difference that was not present in basal measurements[(65, 191)], and suggestive of an altered response to uterine contractions in the feto-placental circulation of these fetuses.

Umbilical artery Doppler has also been used to predict intra-partum outcomes. Early reports demonstrated an association between abnormal umbilical artery Doppler and subsequent evidence of fetal compromise[(192)], leading to the suggestion this technique may be a useful tool for intra-partum surveillance[(193)]. In fetuses with late decelerations evident on CTG

monitoring, an increase in umbilical artery resistance compared to normal controls has been observed[194]. Furthermore, adverse neonatal outcomes are more common in fetuses with abnormal umbilical artery resistance indices[195], even in an appropriately grown cohort[196]. Siristatidis et al observed increased umbilical artery PI during labour induced fetal hypoxia, and found that changes in umbilical artery Doppler correlated with perinatal outcome measures[197]. However, as with other techniques, the use of umbilical artery Doppler as part of a labour admission test has found it to have a poor correlation with neonatal outcomes[198, 199]. This conclusion was further supported by systematic reviews published in 1999[200] and 2010[201], which concluded that Umbilical artery Doppler velocimetry was a poor predictor of adverse perinatal outcome.

Middle cerebral artery

The redistribution of fetal blood flow during periods of hypoxia was first reported in animal studies[202]. This process results in preferential perfusion of the brain, adrenal glands, and cardiac muscle at the expense of less "vital" organs[203]. Evidence of this "brain sparing effect" was subsequently demonstrated in human fetuses by measurement of both umbilical and internal carotid artery Doppler in growth restricted fetuses[66]. Imaging of the intra-cranial circulation was reported by Van den Wiingaared et al in 1989[204]. The middle cerebral arteries, whose waveforms vary significantly to those of the internal carotid arteries[205], are well suited for Doppler investigations due to their anatomical path, which allows insonation of the vessel at a zero degree angle, and therefore the acquisition of accurate flow velocity waveforms. To ensure accuracy, Doppler waveforms must be acquired from a consistent segment of the artery, as waveforms in the proximal and distal regions differ significantly from one another[206]. Excessive pressure on the fetal head during assessment may also result in falsely reduced diastolic flow velocities[207].

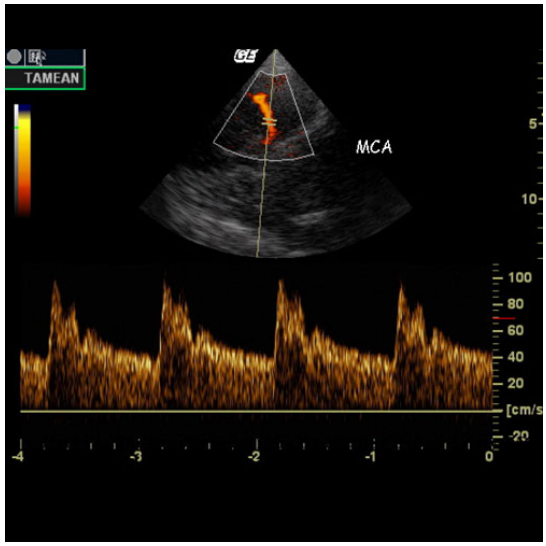


Figure 6 Middle cerebral artery flow velocity waveform acquisition.

In normal pregnancy, middle cerebral artery PI rises to a peak at around 28 weeks gestation, and subsequently undergoes a gradual decline until term[185].

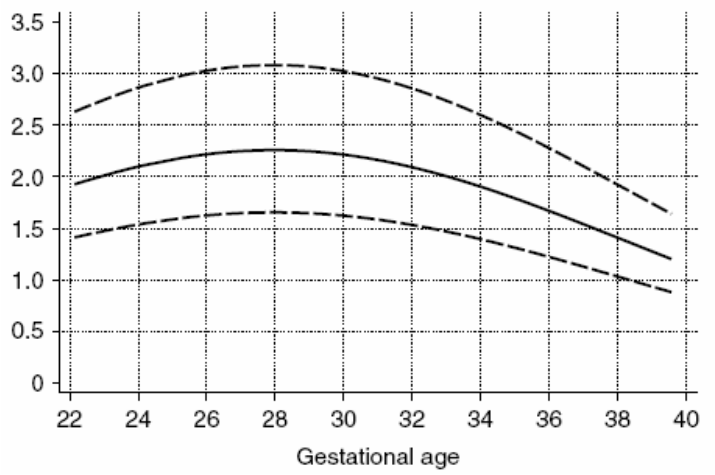


Figure 7 Middle cerebral artery pulsatility index according to gestation. Taken from *Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Prenat Diagn. 2007 Dec;27(13):1251-7.*[185]

Early studies of middle cerebral artery resistance indices in small for gestational age fetuses were contradictory, with published reports suggesting both a reduction[208] and unchanged[209] resistance indices when compared to an appropriately grown cohort. Subsequent reports confirmed that whilst middle cerebral artery resistance was not reduced in all small for gestational age fetuses, its presence identified a cohort at greater risk of adverse neonatal outcome[210, 211], even in cases where the umbilical artery PI remained normal[212, 213].

The role of MCA Doppler in the management of fetal growth restriction and fetal anaemia is now well established in clinical practice[214], but further clinical application of this technique has also been investigated. A reduction in middle cerebral artery resistance has been associated with fetal hypoxia[215], and has also been used to risk stratify pregnancies prior to labour. Cruz-Martinez et al[216] evaluated MCA Doppler indices in a cohort of small for gestational age fetuses, reporting that their use could distinguish a sub-group of SGA fetuses at increased risk of caesarean delivery for non-reassuring fetal status and neonatal acidosis. Leung et al[217] demonstrated that, following successful ECV, the incidence of caesarean delivery for non-reassuring fetal status was more common in fetuses with lower pre-version MCA resistance indices. Middle cerebral artery resistance has also been found to be a significant predictor of meconium stained liquor in postdates pregnancy[218]. A direct relationship between MCA resistance and fetal hypoxia during labour has also been suggested. Kassanos et al[219] compared MCA PI in cohorts of fetuses with Oxygen saturations >30% and <30%. They found significantly lower MCA PI values in the cohort with Oxygen saturation <30%. These findings are suggestive of a relationship between MCA Doppler values and fetal wellbeing, and indicate that MCA Doppler may have value in identifying fetuses at risk of intra-partum fetal compromise.

Umbilical venous flow

In 1984, Gill et al reported evidence of altered umbilical venous flow in growth restricted fetuses[220]. Several reports have confirmed the association of reduced umbilical venous flow with fetal growth restriction[221, 222], and have suggested that alterations in venous flow may occur prior to changes in the umbilical arterial vasculature[223]. A relationship between placental mass and umbilical venous flow has also been demonstrated in some studies[224], although this is not a consistent finding[225]. A correlation between umbilical venous flow and fetal head and abdominal circumferences has also been observed[226].

In normal pregnancy, the umbilical vein exhibits a continuous, non-pulsatile pattern[227]. Although pulsatile umbilical venous flow is now most commonly associated with severe fetal growth restriction[228], it was initially observed in fetuses with pathological CTG abnormalities in labour, that were subsequently delivered by emergency caesarean section[229]. Subsequent investigations have confirmed that the presence of umbilical

venous pulsation is associated with an increased incidence of operative delivery for presumed fetal compromise even in uncomplicated pregnancies[230]. Suggested mechanisms for the development of umbilical venous pulsations include dilatation of the ductus venosus and myocardial decompensation[231, 232].

Longitudinal studies of umbilical venous flow have demonstrated an increase in absolute volume flow with advancing gestation, largely as a result of increases in flow velocity as opposed to changes in umbilical vein diameter[233, 234]. Corrected/normalised blood flow follows a gradual decline with advancing gestation[233, 234].

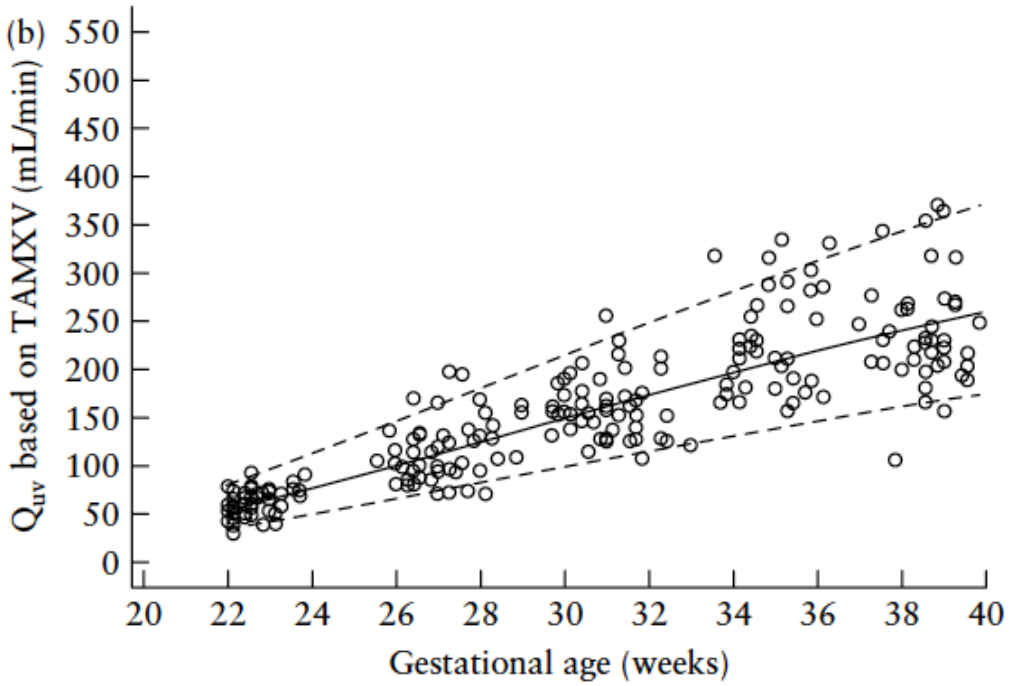


Figure 8 Umbilical venous flow rate according to gestation. Taken from *Flo K, Wilsgaard T, Acharya G. Longitudinal reference ranges for umbilical vein blood flow at a free loop of the umbilical cord. Ultrasound Obstet Gynecol. 2010 Nov;36(5):567-72. doi: 10.1002/uog.7730.*[233]

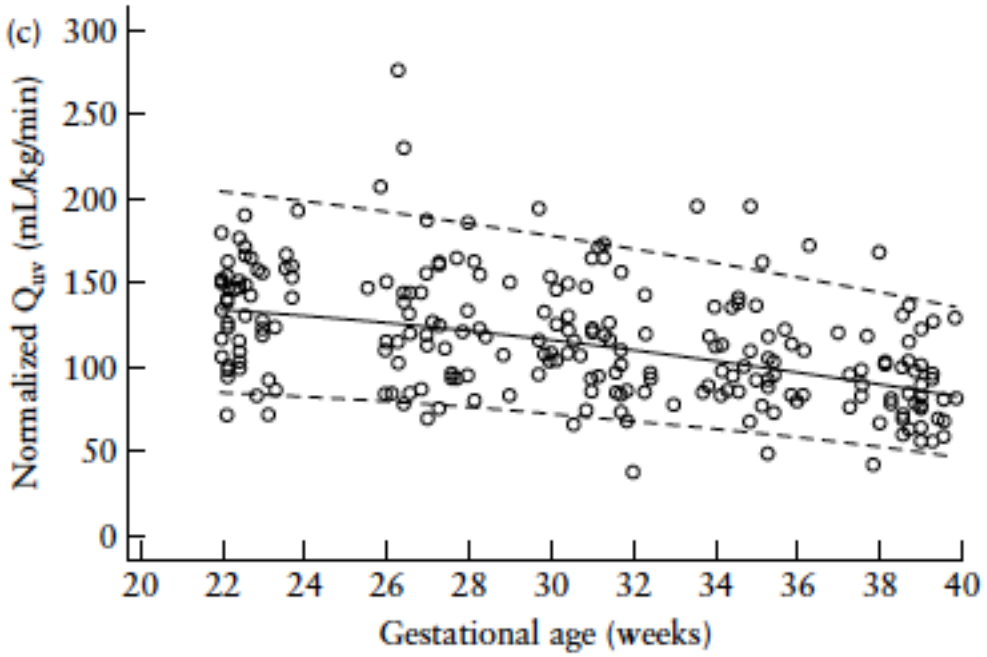


Figure 9 Corrected umbilical venous flow according to gestation. Taken from *Flo K, Wilsgaard T, Acharya G. Longitudinal reference ranges for umbilical vein blood flow at a free loop of the umbilical cord. Ultrasound Obstet Gynecol. 2010 Nov;36(5):567-72. doi: 10.1002/uog.7730.*[(233)]

The value of quantitative measurements of umbilical venous flow in appropriately grown fetuses remains unknown.

Cerebro-umbilical ratio

The cerebro-umbilical (C/U) (also known as the cerebro-placental) ratio is the ratio of the MCA PI to the UA PI. Wladimiroff et al observed in 1987 that in cases of growth restriction, a raised umbilical artery resistance was frequently associated with a reduced internal carotid artery resistance, suggesting the presence of a "brain sparing circulation[(66)]. Furthermore, Arbeille et al reported that in normal pregnancy the cerebral resistance index was normally greater than that of the umbilical artery, resulting in a C/U ratio >1, whereas in pathological pregnancy, complicated by fetal growth restriction or hypertension, the C/U ratio was reduced to <1[(235)]. Subsequently, the C/U ratio was demonstrated to better predict adverse perinatal outcome[(210)] and the small for gestational age fetus[(236)] , than use of either middle cerebral artery or umbilical artery Doppler alone.

Several authors have investigated the value of the C/U ratio as a tool for assessment of fetal wellbeing. Devine et al evaluated a number of techniques used to monitor postdates pregnancy including the C/U ratio, biophysical profile and AFI. They found a C/U ratio of <1.05 to be the most accurate predictor of adverse outcome[237]. Habek et al examined the relationship between both the C/U ratio and fetal biophysical profile, and perinatal outcomes[238]. They reported that the incidence of caesarean delivery was significantly higher in fetuses with a C/U ratio <1. Anteby et al observed that signs of intra-partum fetal compromise in postdates pregnancy were frequently associated with the finding of a raised umbilical artery, and reduced middle cerebral artery resistance indices prior to labour[239]. More recently, Siristatidis et al measured the C/U ratio of fetuses during abnormal CTG recordings, with caesarean section being indicated if the C/U ratio was <1 for more than 2 minutes. They found the use of the C/U ratio led to a significant reduction in rates of caesarean section, with no adverse effect on neonatal outcome reported[240].

Longitudinal reference ranges for the C/U ratio have been published[241]. The C/U ratio gradually rises until around the 34th week, and subsequently undergoes a gradual decline until term.

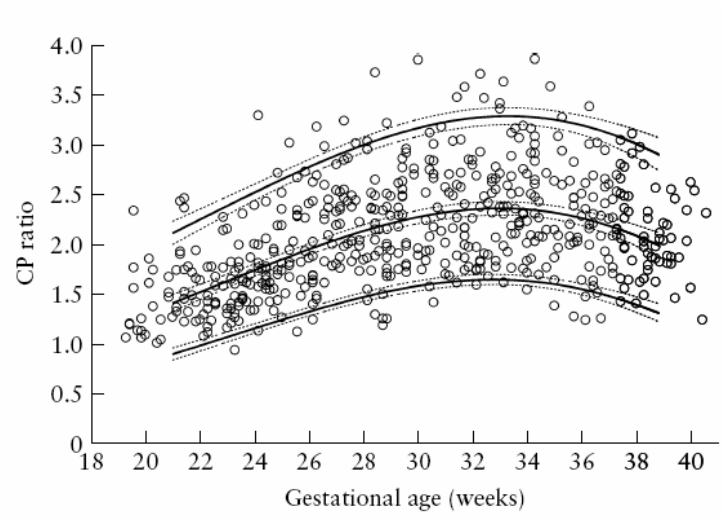


Figure 10 Cerebro-umbilical ratio according to gestation. Taken from *Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol. 2007 Sep;30(3):287-96.*[241]

The Umbilical-Cerebral ratio has also been reported to offer prognostic value in the assessment of placental dysfunction[242], and mathematically this ratio will better accentuate differences in placental function in the most severely affected cases.

Uterine artery

The uterine arteries are responsible for the perfusion of the uterus, and consequently the placenta. Adequate uterine artery flow is therefore critical in maintaining a supply of oxygenised nutrient rich blood to the fetus. Flow velocity waveforms in the uterine arteries have been extensively studied. In 1985, Trudinger et al evaluated uterine artery flow in normal and potentially growth restricted pregnancies. They identified reduced uterine artery diastolic flow velocities in 15/25 pregnancies subsequently delivered of a small for gestational age fetus[243]. In 1986, an association between an increased uterine artery resistance and the subsequent development of stillbirth, growth restriction, and maternal pre-eclampsia was reported[244]. Initially, uterine artery resistance indices were assessed in the second trimester, following the completion of placentation, but later work confirmed that uterine artery waveforms could be accurately acquired in the first trimester[245], and remained predictive of later fetal growth restriction and pre-eclampsia[246]. As a result, uterine artery Doppler has been suggested as a valuable screening mechanism to identify pregnancies at risk of subsequent complications related to placental dysfunction[247].

In normal pregnancy, uterine artery resistance declines with advancing gestation[248].

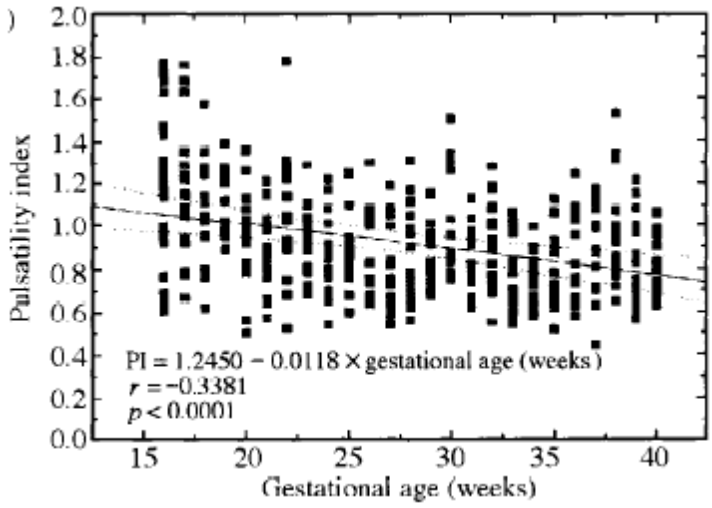


Figure 11 Uterine artery PI according to gestation. Taken from *Weissman A, Jaffa AJ, Lurie S, Har-Toov J, Peyser MR. Continuous wave Doppler velocimetry of the main-stem uterine arteries: the transvaginal approach. Ultrasound Obstet Gynecol. 1995 Jan;5(1):38-43.*[(248)]

The persistence of a high resistance circulation in the uterine arteries has been directly linked with a subsequent reduction in birthweight[(249)], and is hypothesised to occur secondary to sub-optimal trophoblastic invasion and incomplete spiral artery re-modelling[(250)].

There is limited data linking abnormal uterine artery resistance and intra-partum compromise. Olofsson et al examined the increase in uterine artery resistance during contractions in fetuses with positive and negative Oxytocin challenge tests (OCT's). They observed a significantly greater change in uterine artery resistance in OCT positive cases[(71)]. However, further studies by the same author did not demonstrate a difference in flow velocity waveforms of the uterine artery in OCT positive and OCT negative cases, or an association between uterine artery resistance indices and subsequent intra-partum fetal compromise or operative delivery[(251)]. These studies were both limited by the small number of cases included. Further investigation is therefore necessary to establish if changes in uterine artery resistance impact the ability of the fetus to tolerate the stresses of labour.

Amniotic fluid volume

In 1966 Gadd observed that liquor volume, measured by dye dilution technique in 100 pregnancies, was reduced in cases of both severe pre-eclampsia and in utero death[(252)]. Amniotic fluid is initially secreted from amnioblasts, derived from the epiblast of the bi-laminar embryonic disc, but after around 11 weeks gestation, the majority of amniotic fluid is produced via the fetal kidneys as urine, with a significant volume also produced by the fetal lungs. Around this gestation, the fetus will also begin swallowing, and the circulation of amniotic fluid commences. In late gestation, around 1000ml of amniotic fluid will be circulated each day.

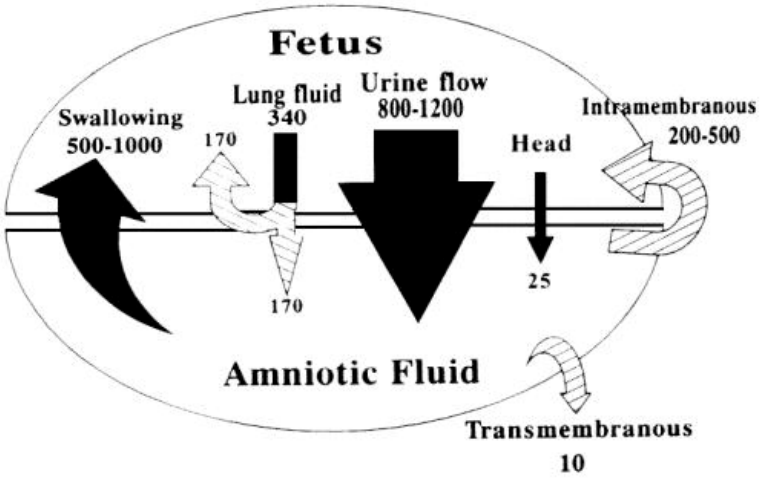


Figure 12 Amniotic fluid circulation. Taken from *Brace RA. Physiology of amniotic fluid volume regulation. Clinical Obstetrics and Gynaecology. 1997 June 40(2) 280-289*[253]

The amniotic fluid volume, dependant to a large extent on fetal urine production[254], can be indicative of placental function[255]. Manning et al reported the strong association between amniotic fluid volume and fetal growth restriction, and also noted increased rates of perinatal morbidity in fetuses with oligohydramnios[256]. In cases of fetal growth restriction, oligohydramnios occurs as a result of reduced fetal urine production[257], which in itself is a manifestation of reduced renal perfusion.

Assessment of amniotic fluid volume has been proposed as a potential method to identify fetuses at risk of compromise in labour. Qualitative assessment of amniotic fluid was a principle component of Manning's original biophysical profile[153], and was later incorporated into the modified biophysical profile. Further studies confirmed that the presence of oligohydramnios was associated with an increased incidence of a subsequent diagnosis of fetal compromise during labour[258-260], and led to suggestions that amniotic fluid volume assessment may represent a good "admission test" to identify fetuses at risk of compromise during labour[261]. However, early randomised trials assessing this technique demonstrated increased caesarean section rates for presumed fetal compromise, without any improvement in decision to delivery times or neonatal outcomes[262]. Other published data also indicated that amniotic fluid volume was only a poor predictor of neonatal outcome[263, 264]. The role of amniotic fluid volume as a predictor of subsequent fetal compromise in labour remains contentious. A meta-analysis published in 1999, supported the assertion that amniotic fluid volume was predictive of subsequent caesarean delivery for fetal compromise, and reduced Apgar score at 5 minutes[265], whilst the most recent study in the

literature concluded the value of oligohydramnios as a predictor of subsequent fetal compromise "remained unanswered"[266].

Meconium stained liquor

The presence of meconium stained liquor during labour has long been associated with concerns regarding fetal wellbeing[267, 268]. However, the passage of meconium, in the presence of a reassuring fetal heart rate pattern, has not been observed to correlate with adverse neonatal outcome[269]. In contrast, when both meconium stained liquor and abnormal fetal heart rate patterns are present, the incidence of adverse neonatal outcomes are increased[270]. The passage of meconium in utero is also associated with increasing fetal maturity, being rare before 34 weeks gestation, and is thought to represent fetal gut maturation[271]. A significant concern in cases of meconium stained liquor, is the development of meconium aspiration syndrome (MAS) in the neonate. This develops in around 5% of infants born with meconium stained liquor[272]. Inhalation of meconium may result in airway obstruction, surfactant inactivation and a chemical pneumonitis, this damage may lead to severe hypoxia and persistent pulmonary hypertension[273]. Identifying which of those births, where meconium stained liquor is present, will be complicated by MAS is difficult, but the associated presence of fetal compromise is a recognised risk factor[274]. An association between reduced middle cerebral artery resistance and the presence of meconium stained liquor has also been observed[218].

Biochemical markers of placental function

A number of biochemical markers have now been associated with placental dysfunction and adverse perinatal outcomes[275]. Perhaps the most established relationship is that of low maternal serum levels of pregnancy associated plasma protein A (PAPP-A) with subsequent fetal growth restriction[276, 277].

Pregnancy associated plasma protein A, was first isolated form the plasma of pregnant women in 1974[278], and was subsequently identified to be of placental origin[279]. However, it wasn't until 1999 that Lawrence et al reported the isolation of an insulin-like growth factor binding protein (IGFBP4) protease, and it's identification as PAPP-A[44]. IGFBP4 binds to

Insulin-like growth factor (IGF) acting as a potent inhibitor of its function. Cleavage of IGFBP4 by PAPP-A, which requires the presence of both IGF-I and IGF-II, thus abolishes its inhibitory effect on IGF[44]. The IGF axis is known to play a critical role in regulating fetal growth[280].

Reduced levels of PAPP-A have been reported in pregnancies complicated by pre-eclampsia and fetal growth restriction[281], leading to suggestions that PAPP-A could be used as a marker of placental function[282]. In normal pregnancy, PAPP-A levels gradually increase throughout gestation[283]. Initially, the clinical utility of PAPP-A was limited to serum screening for Down's Syndrome[284], but observations that a low first trimester PAPP-A level was also associated with fetal growth restriction[285] further expanded the role of PAPP-A in pregnancy screening. More recently, reduced PAPP-A levels have also been associated with an increased risk of intra-partum fetal compromise and emergency delivery[286], as well as alterations in placental villous structure[287].

Human chorionic gonadotrophin (HCG), first isolated from the urine of pregnant women in 1928, formed the basis of the first biochemical pregnancy test[288]. Produced by the syncytiotrophoblast, HCG stimulates progesterone production by the corpus luteum. In normal pregnancy, the level of HCG rises rapidly, peaking around the ninth week, before a gradual decline[289]. Raised levels of HCG are associated with chromosomal anomalies in the fetus[290], and its measurement forms part of first trimester screening for aneuploidy[291]. Reduced levels of HCG have also been associated with an increased risk of fetal growth restriction[292], with some reports suggesting a relationship as strong as that of PAPP-A[293]. An association with intra-partum fetal compromise[294] and cerebral redistribution in the fetus[295] have also been reported, suggesting that evaluation of HCG levels may be indicative of placental function.

Other biochemical markers of placental function include human placental lactogen[296], placental growth factor (PlGF)[297], and others[298]. Low levels of placental growth factor have been strongly linked to pre-eclampsia, with the reduction in circulating PlGF thought to occur secondary to an excess of the anti-angiogenic protein, soluble fms-like Tyrosine Kinase 1 (sFlt1)[299]. An increase in concentrations of sFlt1 in the maternal circulation has also been reported in fetal growth restriction[300]. Given that in many cases, intra-partum fetal compromise is likely to be associated with placental dysfunction[181], it is possible that

assessment of biochemical markers of placental function may help predict fetal compromise.

Other Maternal influences on placental function

Several maternal characteristics have an adverse effect on placental function.

Maternal smoking is associated with an increased incidence of in utero death[301], fetal growth restriction[302], and placental abruption[303]. Absorbed chemicals from cigarette smoke such as Nicotine and Carbon Monoxide have been demonstrated to trigger vasoconstriction within the placenta[304], and significant quantities of Nicotine have been identified in the amniotic fluid and cord blood in fetuses of smoking mothers[305]. Maternal smoking has been observed to have a direct effect on umbilical artery blood flow velocity waveforms, with raised umbilical artery resistance indices evident following maternal cigarette smoke inhalation[306]. In animal studies, Nicotine leads to a reduction in utero-placental blood flow, and subsequent fetal hypoxia and acidosis[307]. However, currently there is no evidence to suggest that maternal smoking is associated with an increased incidence of fetal compromise in labour[308].

Maternal diabetes is also suspected of impacting placental function. The villous basement membrane is reported to be thicker in Diabetics, leading to a reduced diffusion capacity[309]. Furthermore, glycosylated Haemoglobin, present in higher concentrations in diabetics, has a higher Oxygen affinity, resulting in a reduced transfer of Oxygen to fetal Haemoglobin[310]. Delivery by emergency caesarean section is more common in Diabetic mothers[311], and in infants born by emergency delivery due to a non reassuring fetal heart rate pattern, umbilical arterial pH has been found to be lower than in a comparative non-diabetic cohort[312].

Other maternal medical conditions such as chronic hypertension[313] and anti-phospholipid syndrome[314] may also impact placental development, and consequently are associated with an increased incidence of pre-eclampsia and fetal growth restriction[313, 314].

Placental function and subsequent neurodevelopment

Whilst cerebral redistribution is considered protective in utero, preserving blood supply to the fetal brain in cases of placental dysfunction[242, 315], the development of a "brain sparing" circulation may be associated with adverse long term neurological outcomes[316]. Scherjon et al observed that mean IQ score at 5 years of age was significantly lower in infants born with evidence of cerebral redistribution[317], and results at nine years of age demonstrate children who were small for gestational age at birth are more likely to have special educational needs[318]. Even later in life, the impacts of sub-optimal placental function are still evident. Eide et al found that the likelihood of developing schizophrenia increased linearly with decreasing birthweight[319], whilst cardiovascular disease and diabetes are also strongly associated with low birthweight[320] In cases of placental dysfunction, changes in brain architecture have been reported in animal studies,[321, 322], and a reduction in myelination found at autopsy in human fetuses with growth restriction[323]. Even in appropriately grown fetuses, increased cerebral blood flow has been associated with a subsequent reduced performance in neurobehavioral testing[324].

Whilst the association between low birth weight, cerebral redistribution, and subsequent neurodevelopment and long term health are now well established, the current definition of low birth weight is largely an arbitrary one. Currently, evidence regarding the impact of changes in the cerebral circulation in the appropriately grown fetus is limited

Summary

Despite advances in antenatal and intra-partum care, the incidence of cerebral palsy in term pregnancies has not changed over the last 30 years. The development of intra-partum hypoxia, and consequent birth asphyxia, hypoxic-ischaemic encephalopathy and cerebral palsy remain a significant global health problem. Currently, intra-partum management is dominated by the reliance on a monitoring tool (CTG) with poor specificity, high levels of inter-observer variability, and that has been associated with an increased incidence of operative delivery for fetal compromise. Whilst CTG monitoring can be a valuable tool when used effectively, better selection of cases in which it is used would be beneficial. The practice of classifying all pregnancies without identified antenatal complications as "low risk" is probably inappropriate, given that the majority of cases of fetal hypoxia occur within this cohort. This thesis will discuss the investigation of ultrasound assessment as a means of risk stratification of normal, "low risk" pregnancies, prior to labour.

Aims and objectives of thesis

1. To determine the relationship between umbilical artery, middle cerebral artery, uterine artery and umbilical venous blood flow velocity waveforms at term, and subsequent intra-partum and neonatal outcomes.

2. To determine if the relationship between umbilical artery, middle cerebral artery, uterine artery and umbilical venous blood flow velocity waveforms at term and intra-partum and neonatal outcomes is dependent on the proximity of the ultrasound assessment to delivery.

3. To study the association between levels of HCG and PAPP-A, measured during the 1st trimester, with subsequent intra-partum and neonatal outcomes.

4. To develop a “composite risk score”, with the purpose of identifying before labour, those pregnancies at high and low risk of subsequent intra-partum fetal compromise.

5. To determine if maternal Oxygen therapy can influence umbilical artery, middle cerebral artery, uterine artery and umbilical venous blood flow velocity waveforms.

Hypotheses

1. The diagnosis of fetal compromise in labour, and the necessity for emergency operative delivery will be associated with significant variations in the measured flow velocity waveforms:

    - Raised umbilical artery resistance
    - Reduced middle cerebral artery resistance
    - Lower cerebro-umbilical ratio, indicative of increased cerebral perfusion
    - Reduced umbilical venous flow

2. The relationship between ultrasound derived markers of fetal wellbeing and intra-partum and neonatal outcomes will be greatest when the timing of the ultrasound assessment is closely associated with the onset of labour.

3. Alterations in HCG and PAPP-A levels, measured during 1st trimester screening, will be associated with a higher incidence of intra-partum fetal compromise.

4. Maternal Oxygen therapy will result in improved feto-placental blood flow, evidenced by a reduction in umbilical artery resistance and an increased middle cerebral artery resistance.

Chapter 2 – Pilot study

Introduction

Few studies have examined fetal haemo-dynamics in appropriately grown, low risk, term pregnancies. As a consequence, data required for power calculations could not be reliably obtained from previous published manuscripts. Furthermore, it was necessary to confirm that the intended ultrasound assessment could be undertaken in early labour, with the acquisition of satisfactory flow velocity waveforms from the required fetal vessels. An assessment of the intra and inter-observer variability for these measurements in term pregnancy was also required.

In order to address these issues, a pilot study of 100 cases was planned. This case number was chosen as it would result in an acceptable number of Caesarean deliveries for presumed fetal compromise within the pilot study cohort (based on the background rate at our institution of 10%), and would enable recruitment of 50 cases for assessment of intra-observer variability, and 50 cases for assessment of inter-observer variability. Data from this cohort was then used to power a larger study.

Aims

1. To assess the practicality of ultrasound assessment, including fetal biometry, acquisition of satisfactory flow velocity waveforms from the umbilical and middle cerebral arteries, umbilical vein, and uterine artery, in term pregnancies, within three days of delivery.

2. To assess the intra and inter-observer variability of Doppler measurements within this cohort.

3. To generate mean and standard deviation values for each Doppler parameter, enabling an estimate of effect size, and accurate calculation of sample size to achieve statistical power of >0.80.

Methods

One hundred patients were recruited to this prospective observational pilot study at Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare NHS Trust, London, UK. Recruitment took place over a six month period from March 2011 until September 2012. Potential participants were identified on the antenatal ward, delivery suite, and day assessment unit. Each participant was given a copy of the study information sheet (appendix A), and allowed adequate time to read the information and discuss their involvement with their partner, friends, or family. Participants were given the opportunity to ask questions and raise concerns, and to have these adequately addressed by a member of the research team. Participants were then asked to sign a consent form for inclusion in the study (Appendix B).

All recruited participants were approached prior to active labour (cervical dilatation ≤4cm), had singleton pregnancies, and were identified as low risk (defined in Appendix C) based on individual chart review with no fetal concerns identified antenatally. Exclusion criteria included cervical dilatation of >4cm, multiple pregnancy, pre-eclampsia, previously identified fetal growth restriction, known fetal anomaly, evidence of intra-uterine infection, or maternal age <16 years.

All women then underwent an ultrasound examination. Parameters measured included the fetal bi-parietal diameter, head circumference, abdominal circumference, and femur length, thereby allowing an estimated fetal weight to be calculated using Hadlock's formula. Umbilical artery, umbilical vein, and middle cerebral artery Doppler indices (Pulsatility index, Resistance index, Time averaged maximum velocity, end diastolic flow velocity, and maximum velocity) were recorded. Maternal uterine artery Doppler indices were also measured, as was the amniotic fluid index. Patients were positioned in a seated semi-supine position, with the head of the bed elevated at a 45 degree angle to prevent aorto-caval compression. A seated position has been demonstrated to be associated with smaller alterations in cardiac output than the left lateral decubitus position[325] .

Ultrasound technique

All subsequent aspects of this study, reported in the other chapters of this thesis, utilised the techniques described here.

All ultrasound examinations were performed by Dr Tomas Prior, using a GE Voluson e portable ultrasound machine, and an AB2-7RS curvilinear trans-abdominal probe.
Fetal biometric measurements were performed in the following manner, in accordance with the guidelines of the International society of ultrasound in Obstetrics and Gynaecology[326].

For measurement of the fetal *bi-parietal diameter (BPD)*, a cross section of the fetal head at the level of the thalamus was acquired. The midline echo of the falx cerebri was identified, ensuring a symmetrical appearance of both hemispheres, with the cavum septum pellucidum visible anteriorly, and no cerebellum visible posteriorly. The angle of insonation was kept as close to 90 degrees as possible. Calipers were placed on the outer edge of the fetal skull closest to the probe, and the inner edge of the opposite side. In the same plane, the *head circumference (HC)* was measured using the ellipse measurement function of the ultrasound machine.

For measurements of *abdominal circumference (AC)*, a transverse section of the fetal abdomen was obtained. The section was obtained with the stomach and umbilical vein visible, but above the level of the kidneys. The AC was then measured using the ellipse measurement function of the ultrasound machine, placed at the outer surface of the skin.
For measurement of the *femur length*, the femur diaphysis was imaged at an angle of insonation between 45 and 90 degrees, and the longest axis of the ossified diaphysis measured.

Amniotic fluid volume was measured both as the *amniotic fluid index (AFI)* and the *deepest vertical pool (DVP)*. For amniotic fluid index measurement the uterine cavity was divided into four quadrants, and the deepest vertical pool of amniotic fluid in each measured, and added to calculate the AFI. All measurements required the absence of fetal extremities and umbilical cord from the field of view.

Doppler ultrasound

The middle cerebral artery, umbilical artery, umbilical vein, and uterine artery were first identified using colour flow mapping. To prevent the underestimation of velocities, all Doppler flow velocity waveforms were acquired at an angle of insonation as close to zero degrees as possible. If a zero degree angle was not achievable due to fetal positioning, the angle correction function was used to compensate. No flow velocity waveforms were acquired at an angle >30 degrees. The high pass filter was used to limit 'noise' from vessel wall movement. Flow velocity waveforms were not acquired in the presence of uterine contractions or fetal breathing movements. A minimum of 5 consecutive completed waveforms were acquired before resistance indices were calculated using automated software. For each vessel, measurements were repeated in triplicate and the mean value recorded for subsequent data analysis.

Umbilical artery Doppler flow velocity waveforms were recorded at a free loop of cord, in accordance with published guidelines[169]. Although umbilical artery resistance has significant variation along the length of the cord, being greatest at the fetal end[327], it was not always possible to achieve accurate waveform acquisition from this location in full term pregnancies.

For Doppler recordings from the MCA, an axial section of the fetal brain was obtained, and the thalamus and wings of the sphenoid bone identified. Flow velocity waveforms were acquired from the proximal third of the MCA in accordance with published guidelines[169].

To image the uterine artery, a mid-sagittal approach was used, and the uterine artery identified within the para-cervical vascular plexus. Doppler flow velocity waveforms were acquired from the uterine artery at this level, prior to the arcuate artery branches.
Umbilical venous flow velocity was recorded at a free loop of umbilical cord.

Vessel diameter measurements were obtained using grey scale for the umbilical vein and artery, and power Doppler for the middle cerebral artery and uterine artery. For diameter measurements, vessels were imaged in the longitudinal plane, at 90 degrees to the ultrasound beam (or as close to this angle as technically possible). The image was then frozen, and magnified to occupy at least 50% of the field, before the internal diameter was measured using the caliper function. The assessment of flow rate in fetal vessels using this

measurement technique has been demonstrated to be accurate when compared to gold standard methods of in-vivo flow calculation[328]. The umbilical vein and artery diameter were measured at a free loop, the middle cerebral artery at a point one third of its length from its origin on the circle of Willis, and the uterine artery at the apparent cross-over with the external iliac artery prior to the division into the arcuate arteries.
Time averaged maximum velocities, in combination with vessel diameter, were then used to calculate vessel flow rates using the following formula:-

Umbilical venous flow rate (ml/min) = Velocity (cm/s) x 0.3 x Cross sectional area (mm2)

This formula was derived as follows:-

Cross sectional area was calculated using the measured diameter of the vessel and the formula for the area of a circle (πr2)

1 ml/min = 1cm/s/cm2 x 60

A multiplication factor of 0.5 is required to correct for laminar flow in a cylindrical vessel (due to slower flow at the perimeter of the vessel caused by friction with the vessel walls).

1ml/min = 1cm/s/cm2 x 60 x 0.5

1ml/min = 1cm/s/cm2 x 30

As 1cm2 = 100mm2

1ml/min = 1cm/s/mm2 x 30/100

1ml/min = 1cm/s/mm2 x 0.3

For calculation of flow rates the umbilical vein was considered a cylindrical vessel with parabolic laminar flow. Accordingly, the measured umbilical Vmax obtained using pulsed wave Doppler was divided by two to acquire the mean flow velocity within the vessel. The requirement for this correction is derived from Poiseuille's Law and the Navier-Stokes equations. This method of flow calculation is consistent with that used in other published data[234].

Information about the maternal age, ethnicity, parity, booking blood pressure, gestation at onset of labour, body mass index, history of smoking, pre-existing maternal medical

disorders, history of previous fetal growth restriction, stillbirth, or neonatal death was recorded on a proforma (Appendix D).

The data obtained during the ultrasound assessment was not made available to the clinicians responsible for the patient's intra-partum care to ensure that management was not influenced by the ultrasound findings. All parameters were recorded three times to enable intra-observer variability to be calculated, and the mean of these values used for data analysis. Fifty patients were scanned by two trained clinicians to demonstrate inter-observer variability.

After completion of the ultrasound assessment, patients were managed as per local protocols and guidelines. Following delivery, each case was followed up within a 48 hour period by review of case notes and electronic records. Intra-partum outcomes including, CTG abnormalities (classified according to NICE guidelines – see figure 2), meconium stained liquor, fetal blood sampling, hypertension, and pyrexia were recorded. The duration of the 1^{st} stage, 2^{nd} stage, and 3^{rd} stage of labour, as well as the interval between rupture of membranes and delivery was documented. Mode of delivery was recorded for all cases, and if assisted delivery was required, the indication, as recorded by the obstetrician on the operative record, was documented. Neonatal outcomes including birthweight, Apgar scores, umbilical artery and vein pH and base deficit, were recorded on the proforma. Neonatal unit admissions, and the indication for them, were also recorded.

All data was then transferred from the written proforma to a Microsoft Excel 2010 database for storage, and analysed using a combination of SPSS statistics v20 (IBM software) and Prism V (Graphpad software).

The primary outcome of the pilot study was mode of delivery and the presence/absence of a diagnosis of fetal compromise during labour. For the purposes of data analysis, cases were categorized according to mode of delivery (EmLSCS FD = emergency caesarean section for fetal compromise, Instrumental FD = Instrumental delivery for fetal compromise, EmLSCS FTP = emergency caesarean section for Failure to progress/other, Instrumental FTP = Instrumental delivery for prolonged 2^{nd} stage), and ultrasound markers of fetal wellbeing compared between the different mode of delivery groups. Cases were also divided quantitatively according to values of the different ultrasound parameters, and outcomes compared between these groups.

Results

One hundred patients were recruited to this pilot study over a six month period.
Details of maternal demographics were documented from the Obstetric notes (see Table 1).

	Overall
Number of Patients	100
% Nulliparous	68.0% (68/100)
Mean Maternal Age	32.3 (21-47)
Mean BMI	24.6 (17-37)
Mean gestation (weeks)	40.14 (37.00 – 42.00)
Ethnicity (%)	
Caucasian	75% (75/100)
Asian	14% (14/100)
Afro-Caribbean	7% (7/100)
Other	4% (4/100)
Mode of onset of labour (%)	
Induction	79% (79/100)
Spontaneous	21% (21/100)

Table 1. Maternal demographics and mode of onset of labour

Fetal biometry, amniotic fluid index/deepest vertical pool, umbilical and middle cerebral artery and umbilical venous Dopplers were recorded from all cases. Satisfactory flow velocity waveforms from the uterine artery were only achieved in 69% (69/100) cases, due to technical difficulties associated with imaging this vessel by trans-abdominal ultrasound in full term pregnancy. The mean interval between ultrasound assessment and delivery was 1 day (0 - 13 days). Ninety two percent of cases (92/100) had an ultrasound to delivery interval of less than three days. The mean umbilical artery pulsatility index (UA PI) within the study cohort was 0.81 (0.46 – 1.53), with a 5^{th} centile value of 0.55, and a 95^{th} centile value of 1.07. The mean middle cerebral artery pulsatility index (MCA PI) was 1.34 (0.79 - 2.14), with a 5^{th} centile value of 0.93, and a 95^{th} centile value of 1.85. The mean cerebro-umbilical (C/U) ratio within the study cohort was 1.72 (0.87 – 3.15), with a 5^{th} centile value of 1.09, and a 95^{th} centile value of 2.58. The mean umbilical venous (UV) flow rate was 308.9ml/min (32.7 – 622.2) with a 5^{th} centile value of 113.9ml/min and a 95^{th} centile value of 571.1 ml/min. The mean uterine artery PI was 0.78 (0.38 – 2.14), with a 5^{th} centile value of 0.43 and a 95^{th} centile value of 1.27.

Cases were subdivided according to mode of delivery. Twelve percent (12/100) of infants were delivered by emergency caesarean section for presumed fetal compromise, 24%

(24/100) by instrumental delivery for presumed fetal compromise, 11% (11/100) by instrumental delivery for a prolonged 2nd stage, and 38% (38/100) were born by spontaneous vertex delivery (SVD). Fifteen percent were delivered by emergency caesarean section for another indication, predominantly failure to progress in the first stage of labour (12/15). Cases were grouped according to mode of delivery and mean values for each of the Doppler parameters calculated (see table 2).

	EmLSCS FD	Instrumental FD	SVD	Instrumental FTP	LSCS other
UA PI	0.84 (0.65 – 1.06)	0.86 (0.51 – 1.53)	0.81 (0.46 – 1.42)	0.74 (0.63 – 0.84)	0.78 (0.53 – 1.03)
MCA PI	1.24 (0.86 – 1.61)	1.37 (0.87 – 2.14)	1.33 (0.79 – 1.97)	1.56 (1.21 – 1.98)	1.23 (1.03 – 1.61)
C/U ratio	1.52 (0.87 – 1.99)	1.66 (0.94 – 2.58)	1.73 (1.13 – 3.15)	2.11 (1.71 – 2.68)	1.64 (1.14 – 2.40)
UV flow	279.9 (134.6 – 380.9)	275.5 (65.5 – 618.4)	316.0 (57.7 – 571.1)	369.4 (136.0 – 605.2)	323.2 (92.7 – 622.2)
Uterine artery PI	0.84 (0.49 – 1.64)	0.72 (0.43 – 1.03)	0.76 (0.44 – 1.27)	0.96 (0.68 – 2.14)	0.77 (0.38 – 1.21)

Table 2. Doppler parameters according to mode of delivery group.

Infants delivered where the indication was presumed fetal compromise (either caesarean or instrumental) had the highest UA PI, the second lowest MCA PI, lowest C/U ratio, and the lowest UV flow rate.

Cases were then subdivided according to C/U ratio centile groups (<10th centile, 10th-90th centile, >90th centile) (Table 3). These groupings were chosen on the basis of receiver-operator characteristic (ROC) curve analyses, which suggested a C/U ratio <10th centile would result in the optimal balance of sensitivity and specificity.

	C/U = <10th centile	C/U = 10th-90th centile	C/U = >90th centile
Caesarean section Fetal compromise	30.0% (3/10)	10.0% (9/90)	0.0% (0/10)
Fetal compromise diagnosed at any time during labour	70.0% (7/10)	30.0% (27/90)	20.0% (2/10)
SVD	10.0% (1/10)	36.7% (33/90)	40.0% (4/10)
Vaginal delivery of any kind	50.0% (5/10)	76.7% (69/90)	90.0% (9/10)
Caesarean section other indication	20.0% (2/10)	13.3% (12/90)	10.0% (1/10)

Table 3. Delivery outcomes according to C/U ratio centile group.

The same analysis was repeated for the other Doppler parameters (Tables 4-7).

	UA PI = <10th centile	UA PI = 10th-90th centile	UA PI = >90th centile
Caesarean section Fetal compromise	0.0% (0/10)	12.2% (11/90)	10.0% (1/10)
Fetal compromise diagnosed at any time during labour	10.0% (1/10)	34.4% (31/90)	40.0% (4/10)
SVD	50.0% (5/10)	31.1% (28/90)	50.0% (5/10)
Vaginal delivery of any kind	70.0% (7/10)	64.4% (58/90)	80.0% (8/10)
Caesarean section other indication	30.0% (3/10)	12.2% (11/90)	20.0% (2/10)

Table 4. Delivery outcomes according to UA PI centile group.

	MCA PI = <10th centile	MCA PI = 10th-90th centile	MCA PI = >90th centile
Caesarean section Fetal compromise	20.0% (2/10)	11.1% (10/90)	0.0% (0/10)
Fetal compromise diagnosed at any time during labour	50.0% (5/10)	32.2% (29/90)	20.0% (2/10)
SVD	50.0% (5/10)	33.3% (30/90)	30.0% (3/10)
Vaginal delivery of any kind	80.0% (8/10)	61.1% (55/90)	100% (10/10)
Caesarean section other indication	0.0% (0/10)	16.7% (15/90)	0.0% (0/10)

Table 5. Delivery outcomes according to MCA PI centile group.

	UV Flow = <10th centile	UV Flow = 10th-90th centile	UV Flow = >90th centile
Caesarean section Fetal compromise	10.0% (1/10)	12.2% (11/90)	0.0% (0/10)
Fetal compromise diagnosed at any time during labour	40.0% (4/10)	34.4% (31/90)	10.0% (1/10)
SVD	30.0% (3/10)	34.4% (31/90)	40.0% (4/10)
Vaginal delivery of any kind	70.0% (7/10)	64.4% (58/90)	80.0% (8/10)
Caesarean section other indication	20.0% (2/10)	12.2% (11/90)	20.0% (2/10)

Table 6. Delivery outcomes according to UV flow centile group.

	Uterine artery PI = <10th centile	Uterine artery PI = 10th-90th centile	Uterine artery PI = >90th centile
Caesarean section Fetal compromise	0.0% (0/7)	10.9% (6/55)	14.3% (1/7)
Fetal compromise diagnosed at any time during labour	28.6% (2/7)	38.2% (21/55)	14.3% (1/7)
SVD	42.9% (3/7)	43.6% (24/55)	42.9% (3/7)
Vaginal delivery of any kind	71.4% (5/7)	80.0% (44/55)	57.1% (4/7)
Caesarean section other indication	28.6% (2/7)	9.1% (5/55)	28.6% (2/7)

Table 7. Delivery outcomes according to uterine artery PI centile group.

Inter and Intra-observer variability

To assess intra-observer variability, Doppler measurements were repeated after an interval of 30 minutes in a cohort of 50 patients. For assessment of inter-observer variability Doppler measurements were repeated after an interval of 30 minutes, by a different trained practitioner, in a cohort of 50 patients.

Intra and inter-observer variability were assessed using Bland-Altman plots and limits of agreement. Initially a one sample t-test was performed to determine if the mean difference between the measures of UA PI, MCA PI, C/U ratio, and UV flow was significantly different from 0. No significant variation was observed (Table 8).

Intra-observer variability	Mean difference	p =	95% CI
UA PI difference	0.003	0.547	-0.0074 – 0.0138
MCA PI difference	0.001	0.868	-0.0130 – 0.0110
C/U ratio difference	0.006	0.686	-0.0356 – 0.0236
UV flow difference	1.20	0.123	-0.3374 – 2.7436

Table 8. One sample t-test to assess intra-observer variability

Bland-Altman plots were constructed for the UAPI, MCA PI, the C/U ratio, and UV flow (Figure 13).

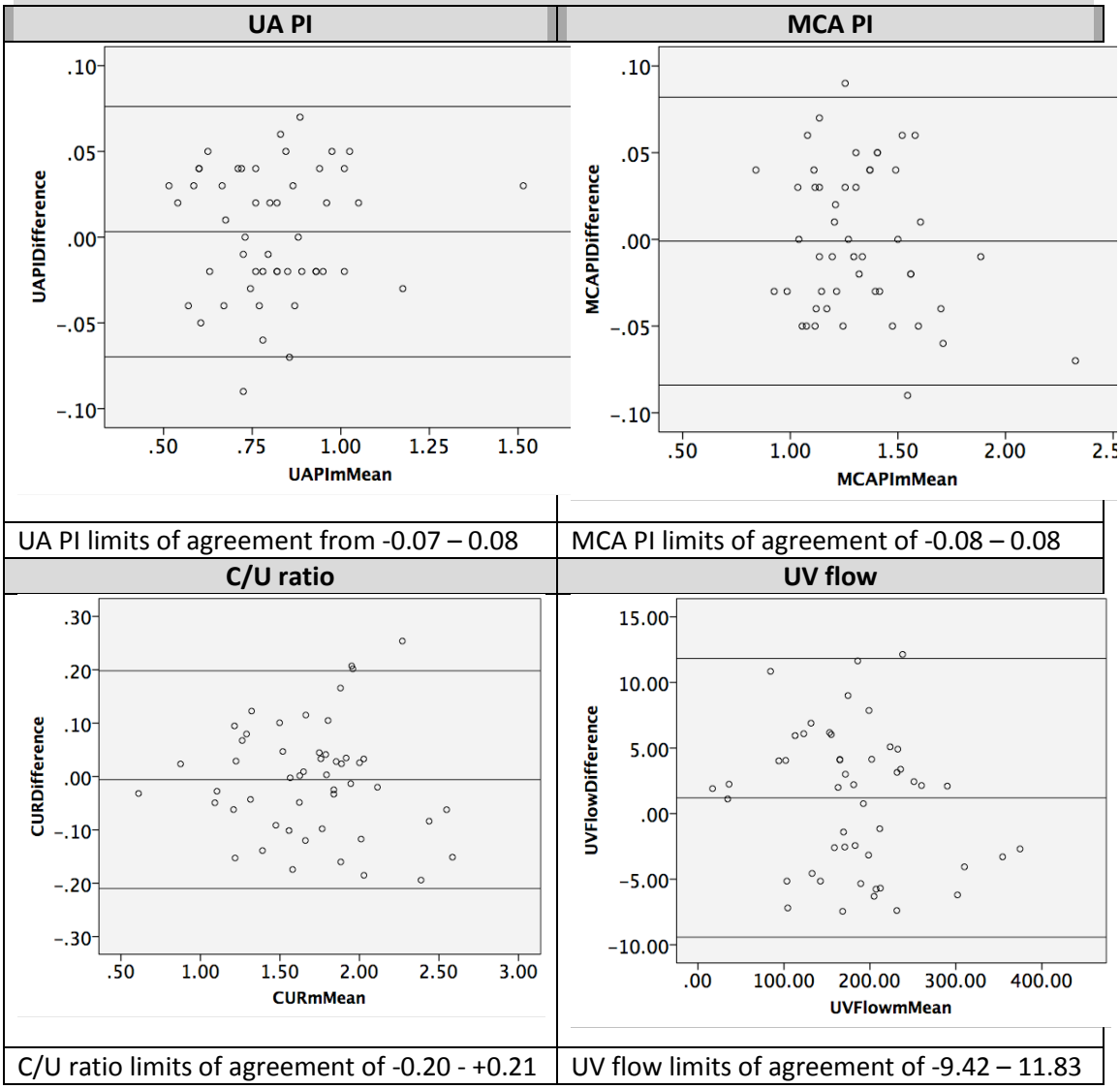


Figure 13. Intra-observer variability - Bland-Altman plots and limits of agreement

Linear regression confirmed there was no proportional bias in the intra-observer variability of either the UAPI, MCA PI, C/U ratio, or UV flow (p = 0.65, 0.12, 0.70, and 0.95 respectively). The same analysis was performed to assess inter-observer variability (Table 10, Figure 14).

Inter-observer variability	Mean difference	p =	95% CI
UA PI difference	-0.003	0.546	-0.0146 – 0.0078
MCA PI difference	0.008	0.302	-0.0072 – 0.228
C/U ratio difference	0.017	0.324	-0.0169 – 0.0503
UV flow difference	1.38	0.335	-1.4674 – 4.2213

Table 9. One sample t-test to assess inter-observer variability

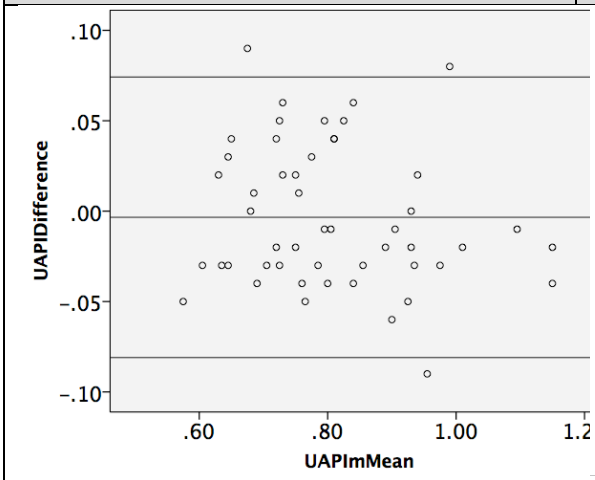
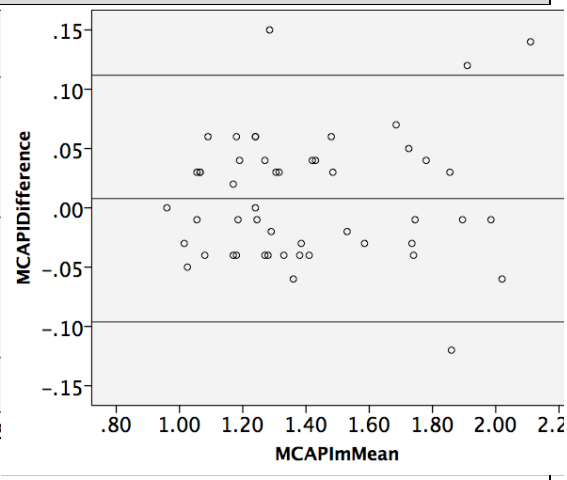
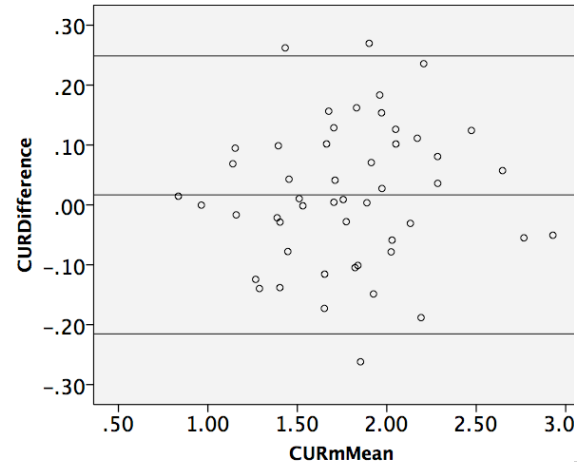
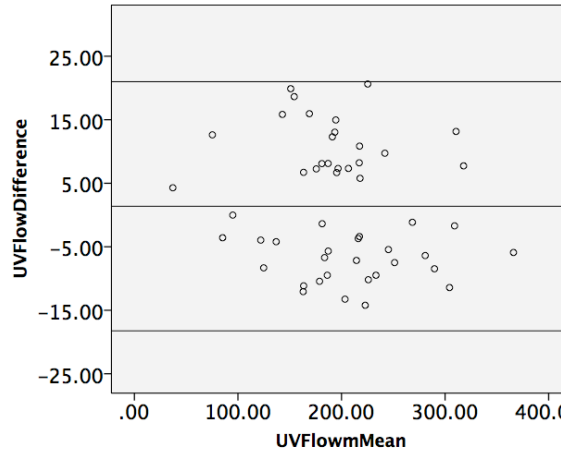
UA PI	MCA PI
	
UA PI limits of agreement -0.08 – 0.07	MCA PI limits of agreement-0.10 – 0.11
C/U ratio	**UV flow**
	
C/U ratio limits of agreement -0.22 – 0.25	UV flow limits of agreement -18.24 – 20.99

Figure 14. Inter-observer variability - Bland-Altman plots and limits of agreement

Linear regression analysis confirmed there was no proportional bias in the inter-observer variability of the UA PI, MCA PI, C/U ratio or UV flow (p = 0.21, 0.61, 0.58, and 0.52 respectively).

Discussion

Power calculation

Few studies have examined fetal haemo-dynamics in appropriately grown, low risk, term pregnancies. The initial aim of the pilot study was to confirm that fetal biometry, umbilical artery, umbilical vein, middle cerebral artery, and uterine artery Doppler indices could be measured at term, within 72 hours of delivery, with acceptable levels of inter-observer and intra-observer variability. Data from the pilot study would then be used to power a larger study.

Fetal biometry, umbilical artery, umbilical Vein, and middle cerebral artery Doppler studies were performed in all 100 patients recruited to the pilot study. Uterine artery Doppler studies were only performed in (69%) 69/100 of patients, due to the technical difficulties associated with imaging the maternal uterine arteries at term.

Is the variation in the C/U ratio sufficient to distinguish those infants at high risk of requiring emergency delivery due to compromise in labour from those at low risk?

The incidence of caesarean section for presumed fetal compromise in fetuses with the lowest C/U ratios (<10^{th} centile) was 0.3 (30%), compared with 0.1 (10%) in those fetuses with C/U ratios ≥10^{th} centile. Power calculation was based on this effect size. A difference in the incidence of Caesareans section for fetal compromise of 20% was also considered a clinically relevant outcome. Assuming a significance level of 0.05,, and unequal sample sizes (between the <10^{th} and ≥10^{th} centile groups), a power of 0.9 could be achieved with a sample size of 50 in the <10^{th} centile group and 450 in the ≥10^{th} centile group.

One hundred participants were recruited to the pilot study over a 6 month period. The data derived from this study enabled sample size calculation for a larger study, with the resultant target of 500 patients. The recruitment rate in the pilot study equalled 16 patients per month, meaning a recruitment period of a further 25 months would be required to reach 500 participants. The rate of recruitment was therefore considered adequate. Of the five Doppler parameters investigated, the C/U ratio showed the greatest variation between the different mode of delivery groups, and as a result was used for power calculation. A C/U ratio <10^{th} centile also resulted in the greatest positive predictive value for emergency

caesarean delivery for presumed fetal compromise, whilst a C/U ratio >90th centile resulted in a 100% negative predictive value within this small cohort. Over 90% of recruited participants had an ultrasound to delivery interval of less than 3 days, suggesting the study design did allow capture of participants sufficiently close to delivery.

Accuracy and reliability of Doppler flow velocity waveforms

Published reference ranges for the UA PI in appropriately grown, term fetuses, such as those of Parra-Cordero et al, suggest a mean UA PI at 40 weeks gestation of 0.74, with a 5th centile value of 0.55 and a 95th centile value of 1.00[185], whilst Acharya et al report a 50th centile value of 0.75, a 5th centile value of 0.51, and a 95th centile value of 1.09[329]. These figures were similar to values reported in this pilot study.

Parra-Cordero et al published reference ranges for the MCA PI in appropriately grown fetuses suggesting a mean MCA PI of 1.14, a 5th centile of 0.83, and a 95th centile of 1.55[185]. Whilst our results differ somewhat from these, other published reference ranges report values very similar to those of this pilot study[330]. The results from all three studies suggest a similar spread in relation to the mean.

Few studies have examined normal ranges of the C/U ratio in appropriately grown term fetuses, but Lam et al studied the C/U ratio in a cohort of normal pregnancies at 41 weeks, and found a mean C/U ratio of 1.63, similar to that found in this pilot study data. Ebbing et al reported a 50th centile value for the C/U ratio at 39 weeks gestation of 1.97, with a 5th centile value of 1.29, and a 95th centile value of 2.88[241]. Similarly, there is limited data reporting UV flow rates in appropriately grown, term pregnancies. Acharya et al reported a 50th centile UV flow rate of 262.7ml/min in a cohort of 130 low risk pregnancies, 5th and 95th centile values were 124.6ml/min and 553.8ml/min respectively. These values are similar to those identified in this pilot study[234]. Published reference ranges for the uterine artery PI suggest a 50th centile value of 0.65, a 5th centile value of 0.47, and a 95th centile value of 0.90[331].

Comparison of Doppler values acquired during the pilot study with published reference ranges suggest that the technique used in the pilot study did result in the acquisition of satisfactory Doppler flow velocity waveforms from all fetal vessels. The limits of agreement reported were consistent with other published data[241]..

The pilot study therefore enabled accurate sample size calculations, confirmed that the required participant number could be recruited within the available time frame, and confirmed that the proposed ultrasound assessment was feasible within 3 days of delivery, and would yield reliable measurements. Following completion of the pilot study, recruitment to achieve the required participant number was commenced.

Chapter 3 - Ultrasound assessment in early labour

Introduction

Following satisfactory completion of the pilot study as described in Chapter 2 of this thesis it was established that recruitment of 500 participants would result in satisfactory power to achieve the aims of this study. This stage of the study would therefore enable conclusions to be drawn regarding the value of a pre-labour ultrasound assessment for the risk stratification of normal pregnancies prior to labour.

Aims

1. To study the relationship between ultrasound derived markers of fetal wellbeing, and subsequent intra-partum and neonatal outcomes.
   Specifically, the following markers of fetal wellbeing were studied:-
   - Fetal weight
   - Amniotic fluid volume
   - Feto-placental and maternal Dopplers
     - Umbilical artery
     - Middle cerebral artery
     - Cerebro-umbilical ratio
     - Umbilical venous flow
     - Uterine artery

2. To ascertain the best ultrasound parameter for the prediction of intra-partum fetal compromise

Methods

Six hundred and four women were recruited to this prospective observational study at Queen Charlotte's and Chelsea Hospital, London, UK. Recruitment took place over a period of 27 months between October 2011 and July 2013. Recruitment was continued beyond the target of 500 participants to allow further sub-group analysis. All study participants gave informed written consent as described in chapter 2. Once consent was obtained, all recruited participants underwent an ultrasound assessment according to the protocol used in the pilot study (described in chapter 2). Data was collected on individual proformas (one per case) (D), before being transferred and stored electronically as a Microsoft Excel spreadsheet. The primary outcome measures were mode of delivery and the presence/absence of a diagnosis of intra-partum fetal compromise. Secondary outcomes included the presence/absence of CTG abnormalities identified during labour, the presence/absence of meconium stained liquor, neonatal outcomes including Apgar scores, umbilical artery pH and base excess at delivery, and neonatal unit admission. CTG recordings were classified according to NICE criteria[332] as normal, suspicious, or pathological by an obstetrician blinded to the ultrasound results. When assessing neonatal outcomes, the incidence of adverse outcomes was compared. For the Apgar score, an adverse outcome was considered to be a score <7 at one or five minutes. This decision was reached following literature review of other studies assessing neonatal outcome, in which a score of <7 is frequently used to define an adverse outcome[333-335]. For umbilical artery pH, an adverse outcome was defined as a pH <7.20. This level was used as a pH of <7.20 on fetal blood sampling is defined as abnormal in current intra-partum guidelines used in the UK[152] and is used to prompt immediate delivery. For umbilical artery base excess, an adverse outcome was considered a base excess of <-8.0. This level has been described as a moderate base deficit in the published literature[336]. Other adverse neonatal outcomes included neonatal unit admission and neonatal encephalopathy. A composite neonatal outcome score was also constructed incorporating multiple neonatal outcome variables. Cases were awarded points for each neonatal outcome variable, with a higher number awarded for greater deviations from normality. An Apgar score of >7 at one minute resulted in 0 points, <7 at one minute 1 point, and <7 at five minutes 2 points. An umbilical artery pH of >7.20 at delivery resulted in 0 points, <7.20 but >7.10 1 point, <7.10 but >7.00 2 points, and <7.00 3 points. An umbilical artery base excess of >-8.0mmol/L at delivery resulted in 0 points, <-8.0 but >-12.0mmol/L 1 point, and <-12mmol/L 2 points. Babies requiring neonatal unit admission were awarded 1 point, and those not requiring admission 0 points.

Data Analysis

All data analysis was conducted using SPSS version 20 (IBM software) and Graphpad Prism version V (Graphpad software).

Distribution of fetal Doppler indices were tested using the D'agostino-Pearson normality test, with a value <0.05 suggestive of a non-normal distribution. Throughout this thesis, medians are reported for variables with non-normal distributions, whilst means are reported for those with normal distributions. Kruskal Wallis and Mann-Whitney U significance testing were used for non-normal distributions, whilst one-way ANOVA (analysis of variance) and independent samples t-tests were used for normal distributions. Dunn's and Bonferroni's multiple comparisons tests were used for non-normal and normal distributions respectively. Both Chi squared testing and relative risk calculations (with 95% confidence intervals) were used for comparing proportions between study groups. Relative risks are more intuitively interpreted and were preferred to odds ratios as the latter has a tendency to overestimate the effect of the independent variable on the dependent variable if the studied outcome is not rare[337]. A threshold of 10% is generally applied to validate the 'rare disease assumption' at which point the odds ratio provides an acceptable approximation of the relative risk[338]. Odds ratios and 95% confidence intervals are reported for logistic regression analyses.

For all significance testing a p-value <0.05 was considered statistically significant. Receiver operator characteristic (ROC) curves were constructed to test the predictive value of each parameter, and to establish optimal levels of sensitivity and specificity.

As this study was designed to identify ultrasound parameters indices of interest, due to the number of comparisons undertaken and to prevent type II error, the Bonferroni correction for multiple comparisons was not applied. Consequently, results of borderline significance must be interpreted with caution.

Results

Maternal demographics and their relationship with Doppler parameters

Details of maternal demographics were documented from the Obstetric notes (see Table 9).

	Overall
Number of Patients	604
% Nulliparous	75.3% (455/604)
Mean Maternal Age (years)	32.3 (16 – 47)
Median BMI (kg/m^2)	24.0 (16 – 42)
Median gestation (weeks)	41.0 (37.0 – 42.0)
Ethnicity (%)	
Caucasian	67.7% (409/604)
Asian	17.4% (105/604)
Afro-Caribbean	10.3% (62/604)
Other	4.6% (28/604)
Mode of onset of labour (%)	
Induction	80.3% (485/604)
Spontaneous	19.7% (119/604)

Table 10. Maternal demographics and mode of onset of labour.

All patients in the study gave birth to live singleton infants. The median time interval between the ultrasound scan and delivery was one day (range 0-14). The time interval between the ultrasound assessment and delivery was less than three days in 96% of cases (581/604). Of the study cohort, 26.5% (160/604) of women were delivered by emergency caesarean, in 43.1% (69/160) of these the indication for delivery was presumed intra-partum fetal compromise. The remaining 56.9% (91/160) of caesarean sections were performed for failure to progress in the 1st stage of labour in 84 cases, following failed instrumental delivery in four cases, and one case each of shoulder presentation, unstable lie, and presumed placental abruption (without fetal compromise). Instrumental deliveries were performed in 34.1% (206/604) of cases, with an indication of presumed fetal compromise in 53.4% (110/206), and failure to progress in the second stage of labour in 46.6% (96/206). Spontaneous vertex deliveries were achieved in 39.4% (238/604) of cases. Cases were sub-divided according to mode of delivery, and maternal characteristics compared between the groups (see Table 10). Nulliparous women formed the majority of all mode of delivery groups with the exception of the SVD group. Significant variation in the mean gestational age of fetuses in each mode of delivery group was also present, with the latest gestation found in cases delivered by caesarean for presumed fetal compromise, and the earliest

gestation in the SVD group. No other statistically significant differences were observed between the different mode of delivery groups.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	ANOVA/χ^2
Number of Patients	604	69	110	238	96	91	
% Nulliparous	75.3% (455/604)	92.8% (64/69)	91.8% (101/110)	49.6% (118/238)	90.6% (87/96)	93.4% (85/91)	<0.001
Mean Maternal Age	32.3 (16 – 47)	32.0 (19 – 42)	32.2 (16 – 44)	32.1 (18 – 47)	32.3 (18 – 43)	33.7 (22 – 46)	0.17
Median BMI	24.0 (16 – 42)	24.0 (19 – 42)	24.0 (18 – 35)	24.0 (17.0 – 38.0)	23.8 (16.0 – 41.0)	24.0 (18.5 – 40.0)	0.13
Median gestation (weeks)	41.0 (37.0 – 42.0)	41.4 (37.7 – 42.0)	41.0 (37.0 – 42.0)	40.6 (37.0 – 42.0)	41.3 (37.6 – 42.0)	41.1 (37.0 – 42.0)	0.01
Ethnicity (%)							
Caucasian	67.7% (409/604)	53.6% (37/69)	73.6% (81/110)	68.9% (164/238)	69.8% (67/96)	65.9% (60/91)	0.60
Asian	17.4% (105/604)	26.1% (18/69)	17.3% (19/110)	13.0% (31/238)	18.8% (18/96)	20.9% (19/91)	0.17
Afro-Caribbean	10.3% (62/604)	14.5% (10/69)	4.5% (5/110)	13.0% (31/238)	6.3% (6/96)	11.0% (10/91)	0.09
Other	4.6% (28/604)	5.8% (4/69)	4.5% (5/110)	5.0% (12/238)	5.2% (5/96)	2.2% (2/91)	0.82
Mode of onset of labour (%)							
Induction	80.3% (485/604)	78.3% (54/69)	78.2% (86/110)	80.7 (192/238)	80.2% (77/96)	83.5% (76/91)	0.99
Spontaneous	19.7% (119/604)	21.7% (15/69)	21.8% (24/110)	19.3% (46/238)	19.8% (19/96)	16.5% (15/91)	0.93

Table 11. Comparison of maternal demographic characteristics of each mode of delivery group.

Women undergoing induction of labour, for indications where there was no immediate suggestion of placental dysfunction, were considered for inclusion in the study. Indications for induction of labour included post-dates pregnancy (<42 weeks gestation) in 59.0% (286/485), a prolonged latent phase of labour in 21.6% (105/485), advanced maternal age (<40 weeks gestation) in 13.0% (63/485), a maternal medical condition (not associated with placental dysfunction) in 3.3% (16/485), large for gestational age (LGA) in 1.0% (5/485), maternal request, previous LGA baby, and previous precipitate labour each in 0.6% (3/485), and one case of induction for unstable lie (0.2%). Maternal demographics and ultrasound parameters were compared between the induction and spontaneous onset of labour groups using binary logistic regression. No significant variation was identified between the two groups. Furthermore, when the incidence of each mode of delivery outcomes was compared between the induction and spontaneous labour group (Table 14) no significant variation was identified.

	Spontaneous	IOL	p =
EmLSCS FD	**12.6% (15/119)**	**11.1% (54/485)**	**0.67**
Instrum FD	**20.2% (24/119)**	**17.7% (86/485)**	**0.58**
SVD	**38.7% (46/119)**	**39.6% (192/485)**	**0.88**
Instrum FTP	**16.0% (19/119)**	**15.9% (77/485)**	**0.98**
EmLSCS other	**12.6% (15/119)**	**15.7% (76/485)**	**0.44**

Table 12. Comparison of mode of delivery outcomes between induction and spontaneous labour groups

The induction of labour group was then sub-categorised according to the indication for induction, and all groups compared to the spontaneous labour group using multinomial logistic regression. It is acknowledged that some of these sub-groups contained few participants and the results should be interpreted with this caveat. The only significant differences identified were a significantly higher maternal age in the advanced maternal age induction group (p = <0.001, odds ratio 2.59, 95% CI 1.89 – 3.57), and a significantly later gestation in the Postdates induction group (p = <0.001, odds ratio 12.05, 95% CI 7.31 – 19.84). No significant variation in ultrasound parameters or mode of delivery outcomes was observed between the groups.

In order to establish whether the ultrasound parameters were influenced by maternal characteristics, potentially confounding the results, the relationship between each maternal characteristic and each ultrasound marker was investigated.

Relationship between parity and ultrasound parameters

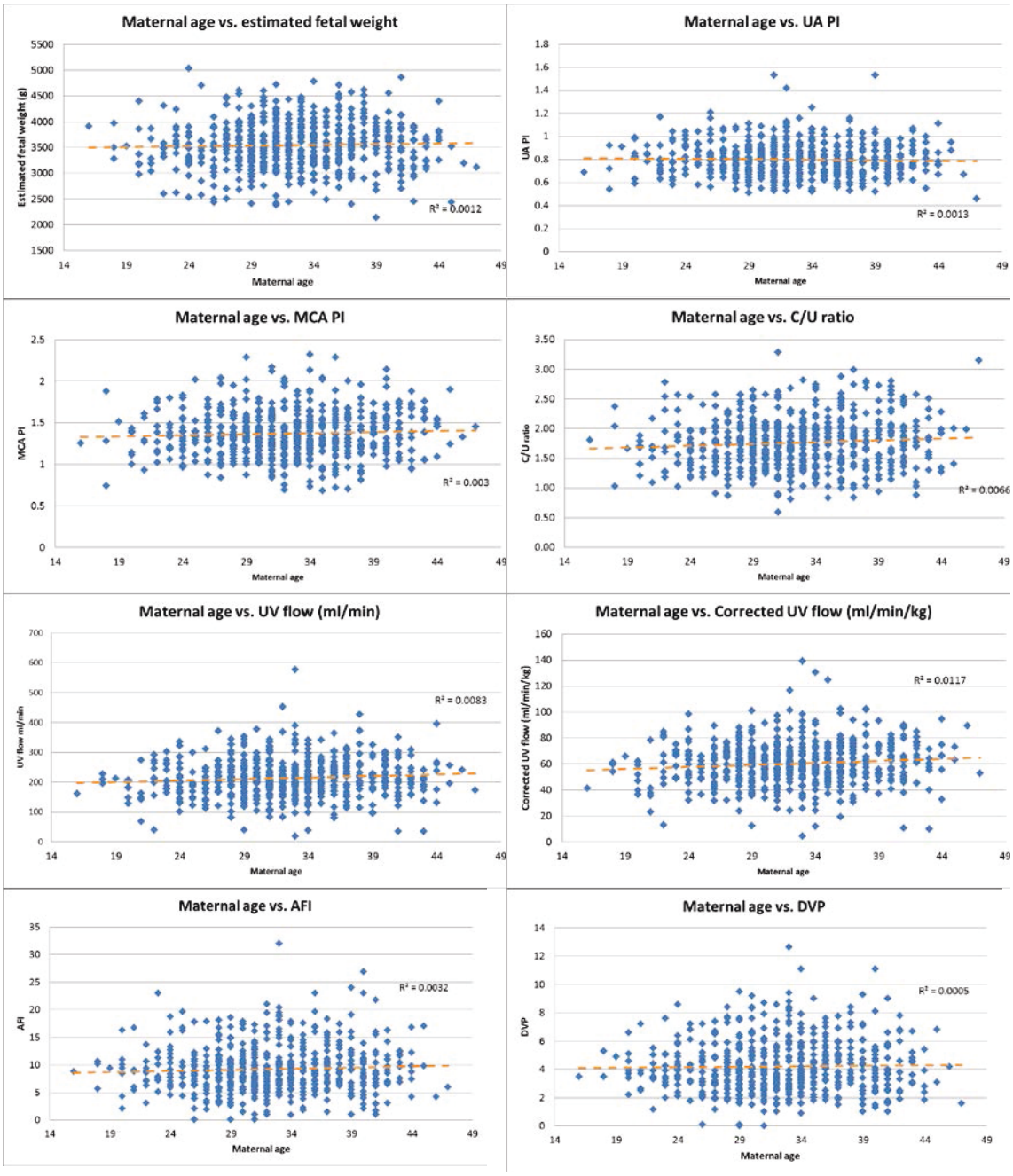
Nulliparous cases were observed to have significantly lower amniotic fluid volume (assessed using AFI), as well as significantly lower MCA PI, C/U ratio, and uterine artery PI (Table 11). Whilst lower umbilical venous flow rates were observed in the nulliparous cohort, this difference did not reach statistical significance.

	Nulliparous	Multiparous	p=
Estimated fetal weight	3551g (2382g – 5037g)	3539g (2136g – 4779g)	0.78
AFI	8.4 (0.0 – 24.0)	9.2 (5.0 – 32.0)	0.01
DVP	3.9 (0.0 – 11.1)	4.0 (1.0 – 12.6)	0.07
UA PI	0.79 (0.51 – 1.53)	0.77 (0.46 – 1.53)	0.13
MCA PI	1.33 (0.68 – 2.32)	1.44 (0.73 – 2.29)	<0.001
C/U ratio	1.72 (0.59 – 3.29)	1.86 (0.94 – 3.15)	<0.001
UV flow	206.4 (34.6 – 577.1)	220.3 (17.9 – 371.0)	0.10
Corrected UV Flow	59.5 (10.1 – 139.0)	62.4 (4.5 – 102.7)	0.12
Uterine artery PI	0.70 (0.30 – 2.13)	0.75 (0.26 – 2.14)	0.04

Table 13. Relationship between parity and ultrasound parameters

Relationship between maternal age and ultrasound parameters

Correlation co-efficient R^2 values <0.1 were observed between maternal age and all ultrasound parameters (Figure 15). The correlation between maternal age and both UV flow and corrected UV flow was statistically significant (p = 0.01 in both cases).



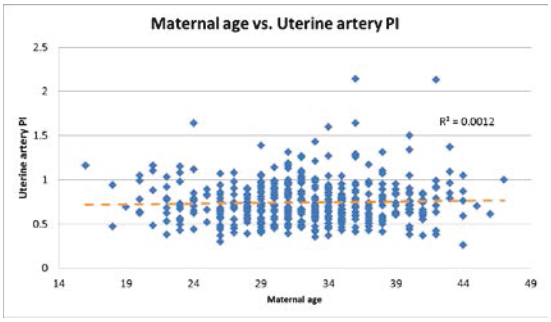
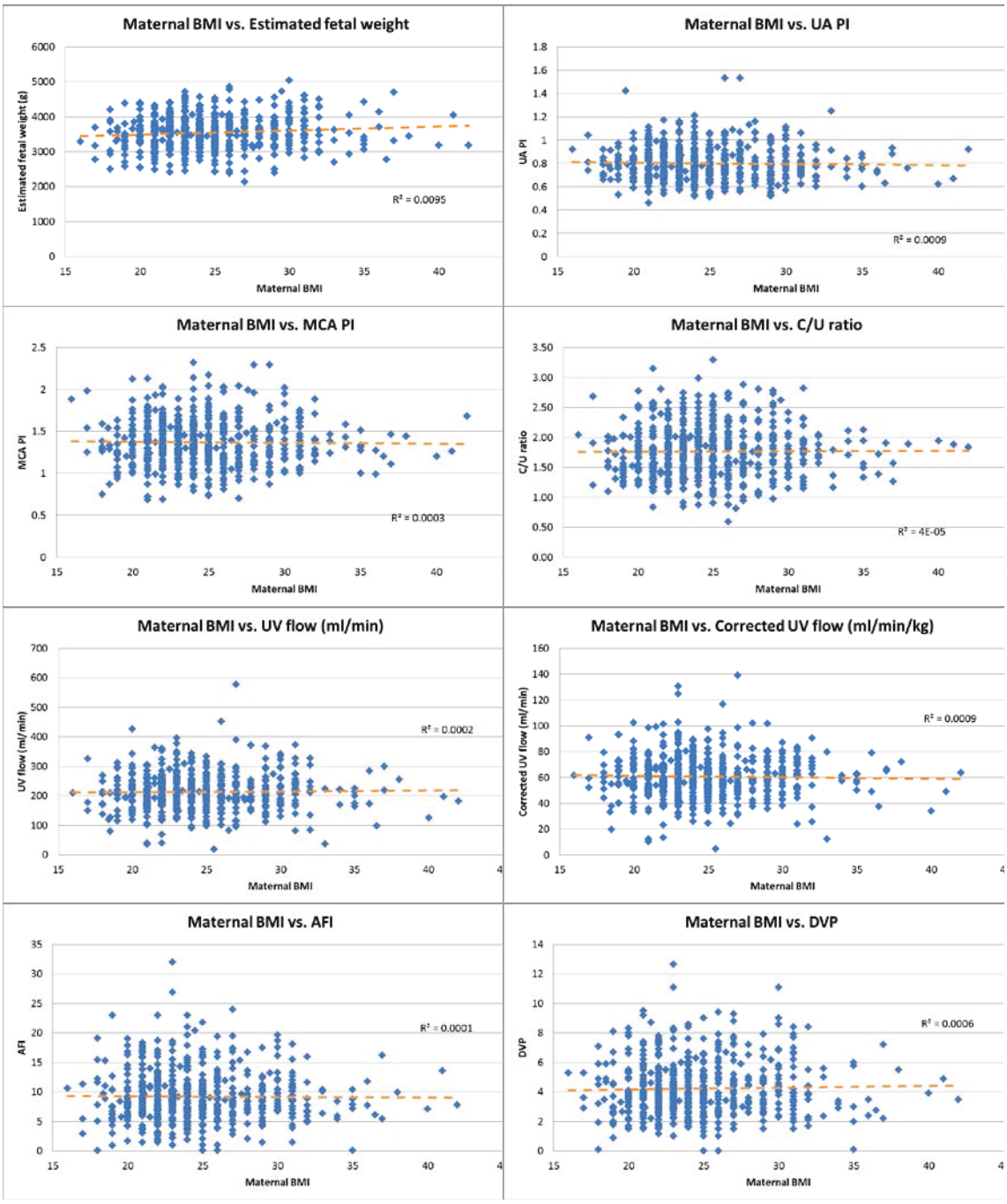


Figure 15 Relationship between maternal age and ultrasound parameters

Relationship between maternal body mass index and ultrasound parameters

Correlation co-efficient R^2 values <0.1 were observed between maternal BMI and all ultrasound parameters (Figure 16). A statistically significant correlation was observed between maternal BMI and EFW (p = 0.04).



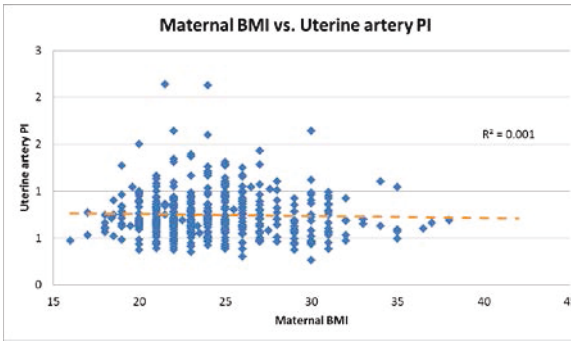
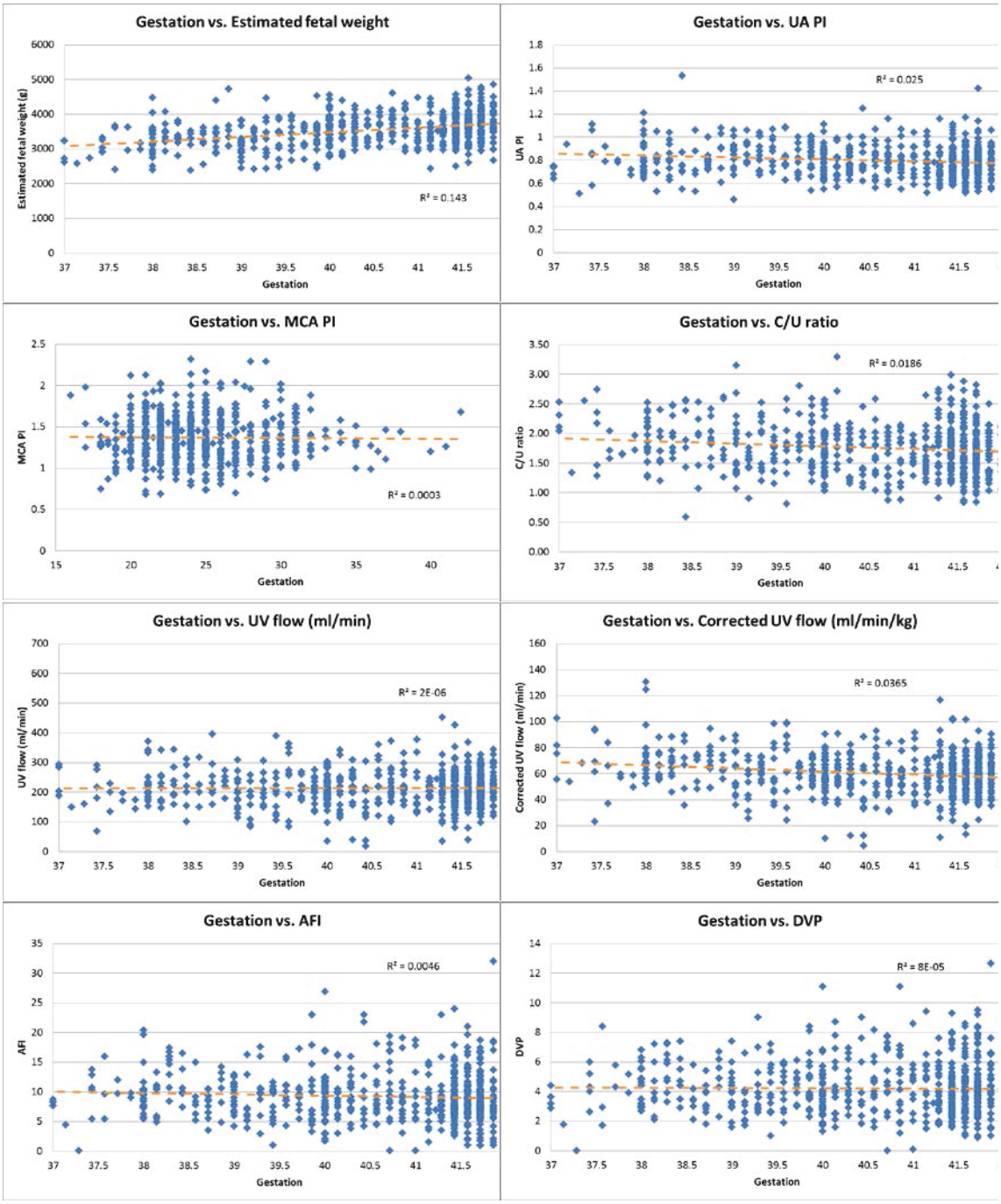


Figure 16. Relationship between maternal BMI and ultrasound parameters

Relationship between gestation and ultrasound parameters

A positive correlation between gestation and estimated fetal weight was observed (R^2 = 0.14, p = <0.001). Correlation co-efficient R^2 values between gestation and all other ultrasound parameters were <0.1. Statistically significant correlations were observed between gestation and UA PI, MCA PI, C/U ratio, corrected UV flow and AFI (p = 0.001, p = <0.001, p = 0.002, p = <0.001, p = 0.03 respectively) (Figure 17).



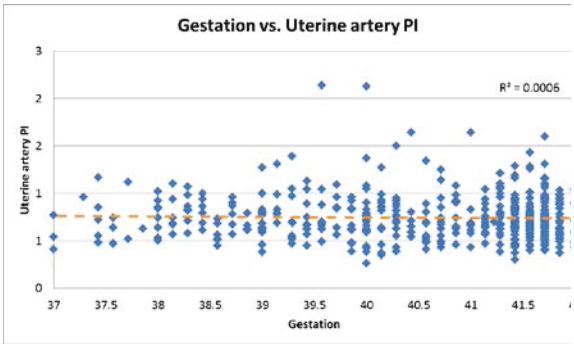


Figure 17. Relationship between gestation and ultrasound parameters

Relationship between ethnicity and ultrasound parameters

Cases were grouped according to ethnicity (Table 12). Significant variations in estimated fetal weight, UA PI and UV flow were observed within the study cohort. Women of Asian ethnicity had the lowest estimated fetal weight and the highest UA PI of any ethnic group. Women with "other" ethnicity had the highest estimated fetal weight. This ethnic group also had the highest UV flow rate, although this difference was no longer significant when UV flow rate was corrected for fetal weight.

	Caucasian	Asian	Afro-Caribbean	Other	p=
UA PI	0.78 (0.46 – 1.42)	0.82 (0.51 – 1.53)	0.78 (0.52 – 1.53)	0.80 (0.56 – 1.08)	0.03
MCA PI	1.35 (0.68 – 2.32)	1.30 (0.87 – 2.29)	1.39 (0.73 – 1.99)	1.37 (0.93 – 1.77)	0.62
C/U ratio	1.78 (0.81 – 3.29)	1.62 (0.59 – 2.68)	1.87 (0.94 – 2.73)	1.78 (1.09 – 2.88)	0.06
UV flow (ml/min)	213.7 (34.6 – 452.4)	201.7 (17.9 – 557.1)	198.7 (37.2 – 325.0)	223.3 (81.6 – 342.1)	0.02
Corrected UV flow (ml/min/kg)	60.4 (11.0 – 130.6)	59.5 (4.5 – 139.0)	58.5 (12.3 – 89.4)	64.1 (23.9 – 86.8)	0.36
Uterine artery PI	0.71 (0.30 – 2.14)	0.68 (0.26 – 1.39)	0.70 (0.38 – 2.13)	0.67 (0.38 – 1.64)	0.76
AFI	8.9 (0.1 – 32.0)	8.0 (0.1 – 19.5)	8.3 (1.0- 24.0)	7.9 (1.7 – 18.7)	0.11
DVP	3.9 (0.0 – 12.6)	3.8 (0.0 – 8.8)	3.7 (1.0 – 9.3)	4.2 (1.3 – 8.6)	0.46
Estimated fetal weight (g)	3601 (2418 – 5037)	3392 (2382 – 4713)	3418 (2136 – 4706)	3637 (3031 – 4542)	<0.01

Table 14. Relationship between maternal ethnicity and ultrasound parameters

Umbilical artery Doppler indices

Umbilical artery pulsatility index (UA PI) was recorded from all 604 cases in the study. Umbilical artery end diastolic flow velocity (UA EDF) and time-averaged maximum flow velocity (UA Tamax) were recorded from 93.4% (564/604) of cases.

Umbilical artery PI

The UA PI had a non-normal distribution in the study population (Skewness = 0.86, Kurtosis = 2.24, D'agostino-Pearson test of normality p = < 0.001). The median UA PI was 0.79 (range = 0.46 – 1.53), with a 10^{th} centile value of 0.63, and a 90^{th} centile value of 0.98.

Cases were grouped according to subsequent mode of delivery and the UA PI compared between these groups (Table 13). Fetuses born by caesarean section for presumed fetal compromise had the highest UA PI. Those born by emergency caesarean for FTP in the 1^{st} stage, and instrumental delivery for a prolonged 2^{nd} stage had the lowest UA PI.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	604	69	110	238	96	91	
UA PI	0.79 (0.46 – 1.53)	0.85 (0.53 – 1.53)	0.79 (0.51 – 1.53)	0.79 (0.46 – 1.42)	0.77 (0.53 – 1.53)	0.75 (0.52 – 1.25)	0.006

Table 15. UA PI according to mode of delivery group.

A Dunn's multiple comparison test was used to compare UA PI values between each mode of delivery group and all others (Table 14).

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	56.07	No
Emergency LSCS FD vs. SVD	62.37	No
Emergency LSCS FD vs. Instrumental FTP	75.71	No
Emergency LSCS FD vs. Emergency LSCS other	102.9	Yes
Instrumental FD vs. SVD	6.296	No
Instrumental FD vs. Instrumental FTP	19.64	No
Instrumental FD vs. Emergency LSCS other	46.79	No
SVD vs. Instrumental FTP	13.34	No
SVD vs. Emergency LSCS other	40.49	No
Instrumental FTP vs. Emergency LSCS other	27.15	No

Table 16. Dunn's multiple comparison test – UA PI

Cases were then divided quantitatively according to their UA PI values as <10th centile, 10th-90th centile, and >90th centile, and the incidence of fetal compromise and vaginal delivery compared between the three groups (Table 15). The highest incidence of caesarean section for presumed fetal compromise, and the highest incidence of a diagnosis of fetal compromise at any time during labour, occurred in fetuses with the highest UA PI values. However, the differences between the UA PI centile groups did not reach statistical significance.

Delivery category	Overall	UA PI <10th Centile	UA PI 10th-90th Centile	UA PI>90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	11.4% (69/604)	8.0% (4/50)	11.1% (55/495)	16.9% (10/59)	0.34	0.47 (95% CI 0.16 – 1.41)
Fetal compromise diagnosed at any time during labour	29.6% (179/604)	22.0% (11/50	29.9% (148/495)	33.9% (20/59)	0.51	0.65 (95% CI 0.35 – 1.22)
SVD	39.4% (238/604)	40.0% (20/50)	38.9% (191/495)	45.8% (27/59)	0.71	0.87 (95% CI 0.56 – 1.36)
Vaginal delivery of any kind	73.5% (444/604)	68.0% (34/50)	74.3% (368/495)	71.2% (42/59)	0.86	0.80 (95% CI 0.60 – 1.05)
Caesarean section other	15.1% (91/604)	24.0% (12/50)	14.5% (72/495)	11.9% (7/59)	0.21	2.02 (95% CI 0.86 – 4.75)

Table 17. Delivery outcomes according to UA PI centile group

A receiver-operator characteristic (ROC) curve was then constructed to see how predictive UA PI was of a subsequent caesarean section for presumed fetal compromise (Figure 18). This resulted in an area under curve (AUC) of 0.61.

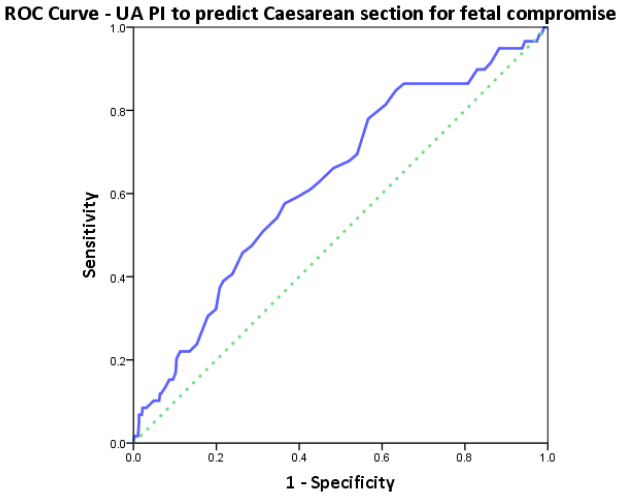


Figure 18. ROC curve – UA PI to predict caesarean section for fetal compromise.

Maternal demographic characteristics in each of the different UA PI centile groups were then compared (Table 16). Significant variation was observed in the gestation at onset of labour, but the absolute difference in gestation between the three groups was small (1.5 weeks). No other significant differences were observed between the different UA PI centile groups.

	Overall	UA PI <10th Centile	UA PI 10th-90th Centile	UA PI >90th Centile	ANOVA/χ^2
Number of Patients	604	50	495	59	
% Nulliparous	75.3% (455/604)	74.0% (37/50)	75.2% (372/495)	78.0% (46/59)	0.97
Mean Maternal Age	32.3 (16 – 47)	32.08 (18 – 47)	32.3 (16 – 46)	31.9 (20 – 44)	0.75
Median BMI	24.0 (16 – 42)	25.0 (19 – 40)	24.0 (16 – 42)	24.0 (17 – 33)	0.31
Median gestation	41.0 (37.0 – 42.0)	41.4 (37 – 42)	41.0 (37 – 42)	39.9 (37 – 42)	0.003
Ethnicity (%)					
Caucasian	67.7% (409/604)	68.0% (34/50)	67.9% (336/495)	66.1% (39/59)	0.99
Asian	17.4% (105/604)	10.0 (5/50)	17.2% (85/495)	25.4% (15/59)	0.15
Afro-Caribbean	10.3% (62/604)	14% (7/50)	10.3% (51/495)	6.8% (4/59)	0.50
Other	4.6% (28/604)	8.0% (4/50)	4.6% (23/495)	1.7% (1/59)	0.31
Mode of onset of labour (%)					
Induction	80.3% (485/604)	82.0% (41/50)	81.2% (402/495)	71.2%(42/59)	0.71
Spontaneous	19.7% (119/604)	18.0% (9/50)	18.8% (93/495)	28.8% (17/59)	0.25

Table 18. Maternal demographics, mode of onset of labour, and birthweight according to UA PI centile group.

Binary logistic regression analysis was performed to control for potential confounding variables. The UA PI was found to vary significantly between fetuses subsequently requiring emergency caesarean section for presumed fetal compromise and those that did not, even when the potentially confounding factors such as gestational age and parity were corrected for (p=<0.001). Similarly, UA PI remained significantly higher in the group of fetuses diagnosed with fetal compromise at any time during labour compared to those without a diagnosis of fetal compromise, even when gestational age and parity were corrected for (p=0.001).

Umbilical artery – Other Doppler Indices

Other Doppler indices of the umbilical artery were also investigated, including UA EDF and UA Tamax. Significant variation in the UA EDF was observed between the mode of delivery groups, whilst the variation in UA Tamax bordered significance (Table 17).

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS FTP	Kruskal Wallis
Number of Patients	564	65	100	222	93	84	
UA End diastolic flow (cm/s)	22.1 (1.4 – 61.2)	20.0 (8.1 – 45.0)	21.5 (8.4 – 43.9)	22.0 (1.4 – 49.1)	23.6 (12.1 – 61.2)	22.8 (13.3 -39.2)	0.007
UA Tamax (cm/s)	33.1 (14.7 – 70.8)	31.1 (17.4 – 59.5)	32.3 (19.0 – 59.0)	33.1 (17.2 – 70.8)	35.0 (18.6 – 60.4)	33.7 (14.7 – 53.7)	0.05

Table 19. UA EDF and UA Tamax mean values according to mode of delivery group.

Cases were then grouped quantitatively according to the UA EDF values as <10th centile, 10th-90 centile, and >90th centile, and the incidence of fetal compromise and vaginal delivery compared between the 3 groups. The highest incidence of caesarean section for presumed fetal compromise occurred in fetuses with the lowest UA EDF. These fetuses were more than five times more likely to require an emergency caesarean delivery for presumed fetal compromise than those with the highest UA EDF values (p = 0.04, RR 5.50, 95% CI 1.28 – 23.70. The same analysis was repeated with cases divided according to UA Tamax centile groups. Fetuses with the lowest UA Tamax values were at significantly increased risk of subsequently requiring delivery by emergency caesarean for presumed fetal compromise (p = 0.01, RR 2.71, 95% CI 1.04 – 7.02).

Umbilical artery Dopplers - summary

UA PI varied significantly between the different mode of delivery groups. Fetuses subsequently delivered by emergency caesarean section for presumed fetal compromise had the highest UA PI values. ROC curve analyses confirmed that UA PI was a significant predictor of subsequent caesarean delivery for presumed fetal compromise. The UA EDF and UA Tamax also had significant variation between the mode of delivery groups. Fetuses with the lowest UA EDF and UA Tamax values were at significantly increased risk of subsequent caesarean delivery for presumed fetal compromise.

Middle cerebral artery Doppler indices

Middle cerebral artery pulsatility index (MCA PI) was recorded from all 604 cases in the study cohort. Middle cerebral artery end diastolic flow velocity (MCA EDF), time-averaged maximum flow velocity (MCA Tamax), and peak systolic velocity (PSV) were recorded from 97.5% (589/604) of cases.

Middle Cerebral artery PI

The median MCA PI in the study cohort was 1.35 (range 0.68 – 2.32), with a 10th centile value of 1.03 and a 90th centile value of 1.72. The MCA PI had a non-normal distribution within the study cohort (Skewness = 0.39, Kurtosis = 0.47, D'agostino-Pearson p=<0.001). Cases were grouped according to the subsequent mode of delivery and the MCA PI compared between these groups (Table 18). Middle cerebral artery PI had significant variation between the mode of delivery groups. Fetuses born by caesarean section for presumed fetal compromise had the lowest MCA PI, whilst those born by SVD, and instrumental delivery for a prolonged 2nd stage had the highest MCA PI.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	604	69	110	238	96	91	
MCA PI	1.35 (0.68 – 2.32)	1.24 (0.69 – 1.74	1.30 (0.68 – 2.17	1.42 (0.73 – 2.32	1.39 (0.70 – 2.04	1.35 (0.86 – 2.29)	<0.001

Table 20. MCA PI according to mode of delivery group.

A Dunn's multiple comparison test was used to compare the MCA PI between each mode of delivery group and all others (Table 19).

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	-37.21	No
Emergency LSCS FD vs. SVD	-96.30	Yes
Emergency LSCS FD vs. Instrumental FTP	-78.22	Yes
Emergency LSCS FD vs. Emergency LSCS other	-51.39	No
Instrumental FD vs. SVD	-59.09	Yes
Instrumental FD vs. Instrumental FTP	-41.01	No
Instrumental FD vs. Emergency LSCS other	-14.19	No
SVD vs. Instrumental FTP	18.08	No
SVD vs. Emergency LSCS other	44.91	No
Instrumental FTP vs. Emergency LSCS other	26.83	No

Table 21. Dunn's multiple comparison test – MCA PI

ROC curve analyses confirmed that MCA PI was a significant predictor of subsequent emergency caesarean section for presumed fetal compromise (Figure 19), with an AUC of 0.63, (95% CI 0.55-0.71 p = 0.001).

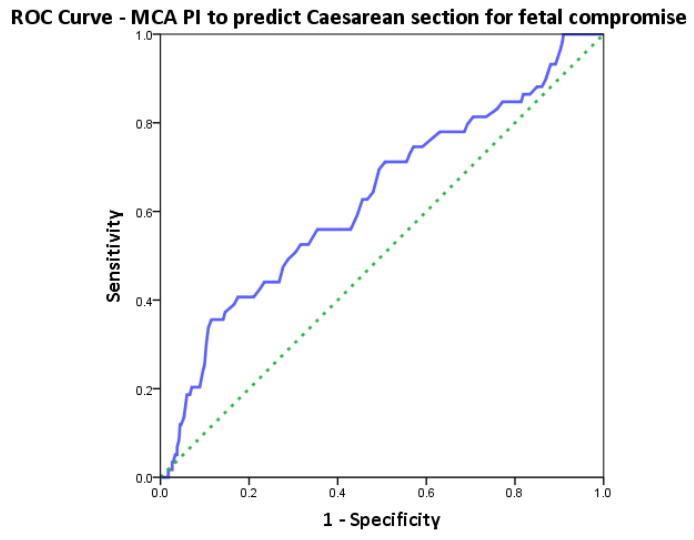


Figure 19. ROC curve – MCA PI to predict caesarean section for fetal compromise.

Cases were then grouped according to MCA PI value as <10th centile, 10th-90th centile, and >90th centile (Table 20). Fetuses with an MCA PI < 10th centile were significantly more likely to be delivered by emergency caesarean section for presumed fetal compromise, as well as

being more likely to be diagnosed with fetal compromise at any time during the labour. These fetuses were also the least likely to be born by a vaginal delivery. Fetuses with the lowest MCA PI were almost five times more likely to require emergency caesarean delivery for presumed fetal compromise.

Delivery category	Overall	MCA PI <10th Centile	MCA PI 10th-90th Centile	MCA PI >90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	11.4% (69/604)	25.9% (14/54)	10.5% (52/496)	5.6% (3/54)	0.002	4.67 95% CI 1.42 – 15.3
Fetal compromise diagnosed at any time during labour	29.6% (179/604)	42.6% (23/54)	30.0% (149/496)	13.0% (7/54)	0.02	3.29 95% CI 1.54 – 7.01
SVD	39.4% (238/604)	38.9% (21/54)	37.3% (185/496)	59.3% (32/54)	0.05	0.66 95% CI 0.44 – 0.98
Vaginal delivery of any kind	73.5% (444/604)	66.7% (36/54)	72.8% (361/496)	87.0% (47/54)	0.42	0.77 95% CI 0.62 – 0.95
Caesarean section other indication	15.1% (91/604)	7.4% (4/54)	16.7% (83/496)	7.4% (4/54)	0.08	1.00 95% CI 0.26 – 3.79

Table 22. Mode of delivery outcomes according to MCA PI centile group.

Maternal demographics were compared between the different MCA PI centile groups (Table 21). Only gestation at onset of labour was found to have significant variation between the different MCA PI centile groups, with fetuses with the lowest MCA PI having the latest mean gestation. Regression analysis was performed to control for this disparity in gestation, as well as for parity. A low MCA PI remained independently associated with both an increased incidence of caesarean section for fetal compromise, and of a diagnosis of fetal compromise at any time during labour.

	Overall	MCA PI <10th Centile	MCA PI 10th-90th Centile	MCA PI >90th Centile	ANOVA/χ^2
Number of Patients	604	54	496	54	
% Nulliparous	75.3% (455/604)	77.8% (42/54)	77.0% (382/496)	57.4% (31/54)	0.28
Mean Maternal Age (years)	32.3 (16 – 47)	32.0 (18 – 42)	32.3 (16 – 47)	32.7 (18 – 45)	0.80
Median BMI (Kg/m^2)	24.0 (16 – 42)	24.0 (18 – 36)	24.0 (17 – 42)	24.5 (16 – 32)	0.98
Median gestation (weeks)	41.0 (37.0 – 42.0)	41.6 (38.1 – 42.0)	40.9 (37.0 – 42.0)	39.9 (37.0 – 41.9)	<0.001
Ethnicity (%)					
Caucasian	67.7% (409/604)	66.7% (36/54)	67.9% (337/496)	66.7% (36/54)	0.99
Asian	17.4% (105/604)	14.8% (8/54)	17.9% (89/496)	14.8% (8/54)	0.78
Afro-Caribbean	10.3% (62/604)	14.8% (8/54)	9.5% (47/496)	13.0% (7/54)	0.41
Other	4.6% (28/604)	3.7% (2/54)	4.6% (23/496)	5.6% (3/54)	0.90
Mode of onset of labour (%)					
Induction	80.3% (485/604)	79.6% (43/54)	80.2% (398/496)	81.5% (44/54)	0.99
Spontaneous	19.7% (119/604)	20.4% (11/54)	19.8% (98/496)	18.5% (10/54)	0.97

Table 23. Maternal demographics, mode of onset of labour, and birthweight according to MCA PI centile group.

Middle cerebral artery – other Doppler indices

Middle cerebral artery EDF, Tamax, and PSV were compared between the different mode of delivery groups (Table 22). Significant variation between the different mode of delivery groups was only observed for MCA EDF. Fetuses delivered by emergency caesarean delivery for presumed fetal compromise had the highest EDF flow velocities.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS FTP	Kruskal Wallis
Number of Patients	589	69	106	233	94	87	
MCA End diastolic flow (cm/s)	15.0 (5.8 – 62.4)	16.5 (7.7 – 33.2)	15.7 (6.6 – 62.4)	14.4 (5.8 – 34.7)	14.9 (8.0 – 36.1)	15.2 (8.3 – 30.0)	0.03
MCA Tamax (cm/s)	29.2 (11.0 – 75.7)	30.9 (13.9 – 75.7)	29.5 (15.1 – 70.8)	29.0 (11.0 – 53.7)	30.2 (17.2 – 53.4)	31.3 (17.3 – 48.6)	0.10
MCA Vmax (cm/s)	56.8 (19.5 – 115.6)	56.4 (24.9 – 86.1)	55.2 (27.7 – 92.7)	56.5 (19.5 – 115.6)	60.5 (33.1 – 84.3)	59.6 (29.3 – 82.1)	0.24

Table 24. MCA Doppler indices according to mode of delivery groups.

Cases were then grouped according to MCA EDF values as <10th centile, 10th-90 centile, and >90th centile, and the incidence of fetal compromise and vaginal delivery compared between the three groups. Fetuses with the highest MCA EDF values were at significantly increased risk of being diagnosed with fetal compromise at some point during labour (RR 0.33, 95% CI 0.11 – 0.97).

Middle cerebral artery Dopplers summary

Of all the MCA Doppler indices analysed, the MCA PI had the greatest variation between the different mode of delivery groups. Those fetuses with the lowest MCA PI had a significantly increased risk of a subsequent diagnosis of fetal compromise, and the need for emergency caesarean section for presumed fetal compromise. Significant variation in MCA EDF was also evident between the different modes of delivery groups.

Cerebro-umbilical ratio

The MCA PI and UA PI were then used to calculate the cerebro-umbilical (C/U). Whilst the U/C ratio may offer better discrimination of the degree of placental dysfunction in the most severely affected babies, the vast majority of the literature relates to the C/U ratio. Furthermore, as this study targeted low risk pregnancies, the number of cases with severe placental dysfunction in which the U/C ratio may offer benefit was likely to be small. The C/U ratio using the following formula:

$$\text{C/U ratio} = \text{MCA PI/UA PI}$$

The median C/U ratio in the study cohort was 1.76 (range = 0.59 – 3.29), with a 10th centile value of 1.24 and a 90th centile value of 2.33. The C/U ratio had a non-normal distribution in the study population (Skewness = 0.37, Kurtosis = 0.14, D'agostino-Pearson p = 0.001) (Figure 20).

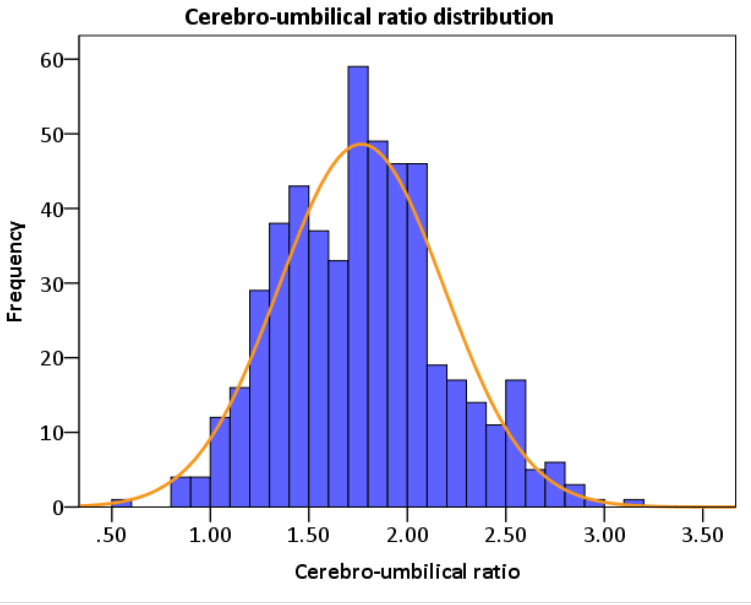


Figure 20. Cerebro-umbilical ratio distribution

Statistically significant variation in the C/U ratio was observed between the different mode of delivery groups (Table 23). Fetuses subsequently delivered by emergency caesarean section for presumed fetal compromise had the lowest C/U ratio, whilst those delivered by caesarean delivery (other indication) had the highest C/U ratio.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	604	69	110	238	96	91	
C/U ratio	1.76 (0.59 – 3.29)	1.56 (0.59 – 2.40)	1.61 (0.83 – 3.29)	1.79 (0.88 – 3.15)	1.79 (1.00 – 2.99)	1.83 (1.04 – 2.78)	<0.001

Table 25. C/U ratio according to mode of delivery group

Using a Dunn's multiple comparison test, the C/U ratio of each mode of delivery group was compared to all other groups (Table 24). The C/U ratio of fetuses born by emergency caesarean for presumed fetal compromise was significantly different to that of all other mode of delivery groups, except the instrumental for presumed fetal compromise group.

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	-49.97	No
Emergency LSCS FD vs. SVD	-102.6	Yes
Emergency LSCS FD vs. Instrumental FTP	-97.90	Yes
Emergency LSCS FD vs. Emergency LSCS other	-100.4	Yes
Instrumental FD vs. SVD	-52.60	No
Instrumental FD vs. Instrumental FTP	-47.93	No
Instrumental FD vs. Emergency LSCS other	-50.47	No
SVD vs. Instrumental FTP	4.676	No
SVD vs. Emergency LSCS other	2.138	No
Instrumental FTP vs. Emergency LSCS other	-2.538	No

Table 26. Dunn's multiple comparison test – C/U ratio

Cases were then grouped according to C/U ratio values as <10th centile, 10th-90th centile, and >90th centile (Table 25). Fetuses with the lowest C/U ratios had significantly higher incidence of emergency caesarean section for presumed fetal compromise, as well as a higher incidence of a diagnosis of fetal compromise at any time during the labour. These fetuses were also significantly less likely to born by spontaneous vertex delivery (SVD). Only one fetus with a C/U ratio >90th centile required delivery by emergency caesarean section for presumed fetal compromise.

Delivery category	Overall	C/U ratio <10th Centile	C/U ratio 10th-90th Centile	C/U ratio >90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	11.4% (69/604)	36.2% (21/58)	9.6% (47/488)	1.7% (1/58)	<0.001	21.00 95% CI 2.92 – 151.0)
Fetal compromise diagnosed at any time during labour	29.6% (179/604)	56.9% (33/58)	28.1% (137/488)	15.5% (9/58)	<0.001	3.67 95% CI 1.93 – 6.96
SVD	39.4% (238/604)	22.4% (13/58)	39.8% (194/488)	53.4% (31/58)	0.03	0.42 95% CI 0.25 – 0.72
Vaginal delivery of any kind	73.5% (444/604)	53.4% (31/58)	74.6% (364/488)	84.5% (49/58)	0.12	0.63 95% CI 0.49 – 0.82
Caesarean section other indication	15.1% (91/604)	10.3% (6/58)	15.8% (77/488)	13.8% (8/58)	0.58	0.75 95% CI 0.28 – 2.03

Table 27. Delivery outcomes according to C/U ratio centile group.

A ROC curve was constructed to assess the use of the C/U ratio to predict emergency caesarean section for fetal compromise (Figure 21). The AUC was 0.67 (95% CI 0.58-0.74, p=<0.001)

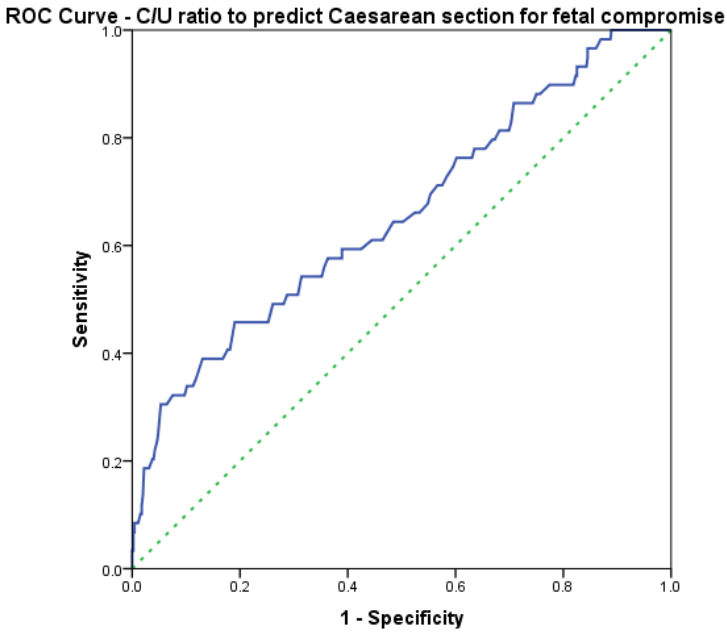


Figure 21. ROC curve – C/U ratio to predict caesarean section for fetal compromise

Maternal demographics were then assessed to determine if any characteristics varied significantly between the C/U ratio centile groups (Table 26). Only the gestation at onset of labour had significant variation between the different C/U ratio centile groups. Regression analysis was used to control for this disparity in gestation, as well as parity, and confirmed that the C/U ratio remained an independent predictor of subsequent caesarean section for presumed fetal compromise.

	Overall	C/U ratio <10th Centile	C/U ratio 10th-90th Centile	C/U ratio >90th Centile	ANOVA/ χ^2
Number of Patients	604	58	488	58	
% Nulliparous	75.3% (455/604)	89.7% (52/58)	75.6% (369/488)	58.6% (34/58)	0.15
Mean Maternal Age	32.3 (16 – 47)	32.0 (18 – 42)	32.2 (16 – 46)	33.5 (18 – 47)	0.23
Median BMI	24.0 (16 – 42)	25.0 (17 – 33)	24.0 (16 – 42)	24.0 (17 – 31)	0.77
Median gestation (weeks)	41.0 (37.0 – 42.0)	41.4 (37.0 – 42.0)	41.0 (37.0 – 42.0)	40.0 (37.0 – 41.9)	0.002
Ethnicity (%)					
Caucasian	67.7% (409/604)	65.5% (38/58)	67.4% (329/488)	72.4% (42/58)	0.89
Asian	17.4% (105/604)	17.2% (10/58)	18.2% (89/488)	10.3% (6/58)	0.40
Afro-Caribbean	10.3% (62/604)	12.1% (7/58)	10.0% (49/488)	10.3% (6/58)	0.90
Other	4.6% (28/604)	5.2% (3/58)	4.3% (21/488)	6.9% (4/58)	0.67
Mode of onset of labour (%)					
Induction	80.3% (485/604)	75.9% (44/58)	79.7% (389/488)	89.7%(52/58)	0.67
Spontaneous	19.7% (119/604)	24.1% (14/58)	20.3% (99/488)	10.3% (6/58)	0.20

Table 28. Maternal demographics, mode of onset of labour, and birthweight according to C/U ratio centile group

Cerebro-umbilical ratio summary

Significant variation in the C/U ratio was observed between the different mode of delivery groups. The C/U ratio was confirmed to be a significant independent predictor of a subsequent diagnosis of fetal compromise, as well as for caesarean section for presumed fetal compromise. Higher C/U ratios were also found to be associated with an increased incidence of vaginal delivery. Fetuses with the lowest C/U ratios were 21 times more likely to require emergency caesarean delivery for presumed fetal compromise than those with the highest C/U ratios.

Umbilical Vein

Umbilical venous flow velocity was recorded in all 604 cases in the study cohort. Umbilical vein diameter was recorded from 602 cases in the study. In two cases the umbilical vein could not be adequately visualised in longitudinal section to enable accurate measurement of its diameter. The median umbilical venous flow velocity was 16.5cm/s (range 8.7 – 29.0) with a 10th centile value of 13.1cm/s and a 90th centile value of 20.3cm/s. Umbilical venous flow velocity had a non-normal distribution in the study population (Skewness = 0.38 , Kurtosis = 0.70, D'agostino-Pearson p =<0.001). The median umbilical vein diameter was 7.4mm (range 2.8 – 10.2) with a 10th centile value of 6.3mm and a 90th centile value of 8.3mm. Umbilical vein diameter also had a non-normal distribution (Skewness = -0.93, Kurtosis = 3.70, D'agostino-Pearson p =<0.001). These values resulted in a median umbilical venous flow rate of 210.1 ml/min (range 17.9 – 577.1), with a 10th centile value of 140.4ml/min and a 90th centile value of 292.8ml/min. Umbilical venous flow rate had a non-normal distribution (Skewness = 0.52, Kurtosis = 2.35 , D'agostino-Pearson p = <0.001).

Significant variation in the umbilical venous flow velocity, umbilical vein diameter, and umbilical venous flow rate was observed between the different mode of delivery groups (Table 27). Fetuses born by emergency caesarean section for presumed fetal compromise had the lowest umbilical venous flow velocity and the lowest umbilical venous flow rate of any mode of delivery group. Fetuses born by instrumental delivery for a prolonged 2nd stage had the greatest umbilical venous flow velocity (in conjunction with the caesarean 'other' group), the largest umbilical vein diameter (in conjunction with the SVD and caesarean 'other' group), and the largest umbilical venous (UV) flow rate.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	604	69	110	238	96	91	69
UV Flow velocity (cm/s)	16.5 (8.7 – 29.0)	15.7 (8.7 – 21.8)	16.9 (10.5 – 25.4)	16.5 (10.1 – 25.9)	17.0 (12.2 – 24.0)	17.0 (9.3 – 29.0)	0.01
	Overall	**Emergency LSCS FD**	**Instrumental FD**	**SVD**	**Instrumental FTP**	**Emergency LSCS FTP**	**Kruskal Wallis**
Number of Patients	602	69	110	237	96	90	69
UV diameter (mm)	7.4 (2.8 – 10.2)	7.3 (5.2 – 9.0)	7.1 (3.3 – 10.2)	7.4 (2.9 – 9.4)	7.4 (4.7 – 9.7)	7.4 (2.8 – 9.4)	0.003
UV Flow rate (ml/min)	210.1 (17.9 – 577.1)	190.2 (83.4 – 342)	198.6 (39.3 – 452.4)	216.8 (34.6 – 377.6)	219.1 (81.6 – 363.1)	213.7 (17.9 – 577.1)	<0.001

Table 29. Umbilical venous diameter, flow velocity, and flow rate according to mode of delivery group

Using Dunn's multiple comparison test, the UV flow rate of each mode of delivery group was compared to all others (Table 28).

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	-28.67	No
Emergency LSCS FD vs. SVD	-70.96	Yes
Emergency LSCS FD vs. Instrumental FTP	-101.6	Yes
Emergency LSCS FD vs. Emergency LSCS other	-77.84	No
Instrumental FD vs. SVD	-42.29	No
Instrumental FD vs. Instrumental FTP	-72.90	Yes
Instrumental FD vs. Emergency LSCS other	-49.17	No
SVD vs. Instrumental FTP	-30.61	No
SVD vs. Emergency LSCS other	-6.882	No
Instrumental FTP vs. Emergency LSCS other	23.72	No

Table 30. Dunn's multiple comparison test – UV flow

Cases were then grouped according to UV flow rate as <10th centile, 10th-90th centile, and >90th centile (Table 29). Fetuses with the lowest UV flow rates were twice as likely to be diagnosed with fetal compromise during labour as those with the highest UV flow rates. No other significant differences in the mode of delivery outcomes were identified.

Delivery category	Overall	UV Flow <10th Centile	UV Flow 10th-90th Centile	UV Flow >90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	11.5% (69/602)	18.3% (11/60)	10.8% (52/482)	10.0% (6/60)	0.25	1.83 95% CI 0.72 – 4.64
Fetal compromise diagnosed at any time during labour	29.7% (179/602)	43.3% (26/60)	29.3% (141/482)	20.0% (12/60)	0.06	2.17 95% CI 1.21 – 3.88)
SVD	39.4% % (237/602)	31.7% (19/60)	41.3% (199/482)	31.7% (19/60)	0.32	1.00 95% CI 0.59 – 1.69
Vaginal delivery of any kind	73.6% (443/602)	65.0% (39/60)	75.7% (365/482)	65.0% (39/60)	0.47	1.00 95% CI 0.77 – 1.30
Caesarean section other indication	15.0% % (90/602)	16.7% (10/60)	13.5% (65/482)	25.0% (15/60)	0.09	0.67 95% CI 0.33 – 1.36

Table 31. Mode of delivery outcomes according to UV flow centile group

Umbilical venous flow was found to have a significant positive correlation with birthweight (Spearman r^2 = 0.42, 95% CI 0.35 – 0.49, p = <0.001), so the data was re-analysed using UV flow values corrected for birthweight.

Corrected UV flow had a median value of 60.2ml/min/kg (4.5-139.0), with a 10th centile value of 41.1ml/min/kg and a 90th centile value of 79.2ml/min/kg. Corrected UV flow had a

non-normal distribution within the study cohort (Skewness = 0.33, Kurtosis = 2.10, D'agostino-Pearson p = <0.001) (see figure).

Significant variation was observed in the corrected UV flow rate between the different mode of delivery groups (Table 30). The lowest corrected UV flow rate was found in the group of fetuses delivered by emergency caesarean section for presumed fetal compromise, whilst the highest rate was found in the group of fetuses delivered by instrumental delivery for failure to progress in the 2nd stage.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS FTP	Kruskal Wallis
Number of Patients	609	69	110	237	96	90	69
Corrected UV flow rate (ml/min/kg)	60.2 (4.5 – 139.0)	57.0 (24.2 – 130.6)	58.9 (12.4 – 116.6)	62.2 (11.0 – 102.7)	63.8 (23.9 – 99.3)	57.0 (4.5 – 139.0)	0.02

Table 32. Corrected umbilical venous flow rate according to mode of delivery group

Using a Dunn's multiple comparison test, the corrected UV flow rate of each mode of delivery group was compared to all others (Table 31). A significant difference in corrected UV flow was only found between fetuses delivered by emergency caesarean for presumed fetal compromise group and those delivered by instrumental delivery for a prolonged 2nd stage.

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	-34.23	No
Emergency LSCS FD vs. SVD	-65.27	No
Emergency LSCS FD vs. Instrumental FTP	-82.03	Yes
Emergency LSCS FD vs. Emergency LSCS other	-40.45	No
Instrumental FD vs. SVD	-31.04	No
Instrumental FD vs. Instrumental FTP	-47.79	No
Instrumental FD vs. Emergency LSCS other	-6.212	No
SVD vs. Instrumental FTP	-16.76	No
SVD vs. Emergency LSCS other	24.83	No
Instrumental FTP vs. Emergency LSCS other	41.58	No

Table 33. Dunn's multiple comparison test – corrected UV flow

Cases were then grouped according to corrected UV flow rate values as <10th centile, 10th-90th centile, and >90th centile (Table 32). Fetuses with the lowest corrected UV flow rates were significantly more likely to be diagnosed with fetal compromise during labour than those with the highest corrected UV flow rates.

Delivery category	Overall	Corrected UV Flow <10th Centile	Corrected UV Flow 10th-90th Centile	Corrected UV Flow >90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	11.5% (69/602)	16.7% (10/60)	11.2% (54/482)	8.3% (5/60)	0.38	2.00 95 % CI 0.73 – 5.50
Fetal compromise diagnosed at any time during labour	29.7% (179/602)	41.7% (25/60)	29.3% (141/482)	21.7% (13/60)	0.12	1.92 95% CI 1.09 – 3.39
SVD	39.4% % (237/602)	33.3% (20/60)	39.4% (190/482)	45.0% (27/60)	0.60	0.74 95% CI 0.47 – 1.17
Vaginal delivery of any kind	73.6% (443/602)	65.0% (39/60)	74.7% (360/482)	73.3% (44/60	0.71	0.89 95% CI 0.70 – 1.13
Caesarean section other indication	15.0% % (90/602)	18.3% (11/60)	14.1% (68/482)	18.3% (11/60)	0.56	1.00 95% CI 0.46 – 2.15

Table 34. Delivery outcomes according to corrected umbilical venous flow rate centile group

When maternal demographics were compared between the three corrected UV flow rate centile groups, significant variation was observed only in the mean gestational age (Table 33). Binary logistic regression was used to adjust for this potential confounding factor, the variation in corrected UV flow rate between fetuses with and without a diagnosis of fetal compromise in labour remained significant.

	Overall	Corrected UV Flow <10th Centile	Corrected UV Flow 10th-90th Centile	Corrected UV Flow >90th Centile	ANOVA/χ^2
Number of Patients	602	60	482	60	
% Nulliparous	75.4% (454/602)	80.0% (48/60)	75.3% (363/482)	71.7% (43/60)	0.87
Mean Maternal Age	32.4 (16 – 47)	31.4 (20 – 44)	32.3 (16 – 47)	33.7 (22 – 46)	0.08
Median BMI	24.0 (16.0 – 42.0	24.0 (18.4 – 40.0)	24.0 (16.0 – 42.0)	24.0 (17.0 – 33.0)	0.98
Median gestation	41.0 (37.0 – 42.0)	41.0 (37.4 – 42.0)	41.1 (37.0 – 42.0)	40.1 (37.0 – 42.0)	0.007
Ethnicity (%)					
Caucasian	67.8% (408/602)	66.7%(40/60)	68.3% (329/482)	65.0% (39/60)	0.95
Asian	17.4% (105/602)	16.7% (10/60)	16.6% (80/482)	25.0% (15/60)	0.33
Afro-Caribbean	10.1% (61/602)	11.7% (7/60)	10.4% (50/482)	6.7% (4/60)	0.64
Other	4.7% (28/602)	5.0% (3/60)	4.8% (23/482)	3.3% (2/60)	0.88
Mode of onset of labour (%)					
Induction	80.4% (484/602)	70.0% (42/60)	81.1% (391/482)	85.0% (51/60)	0.61
Spontaneous	19.6% (118/602)	30.0% (18/60)	18.9% (91/482)	15.0% (9/60)	0.13

Table 35. Maternal demographics according to corrected UV flow centile group

Umbilical vein summary

Significant variation was observed in umbilical venous flow velocity, umbilical vein diameter, and umbilical venous flow rate (both corrected and uncorrected) between the different mode of delivery groups. The variation in umbilical venous flow was predictive of a subsequent diagnosis of fetal compromise in labour.

Uterine artery Doppler

Uterine artery flow velocity waveforms were recorded from 460 cases. In 144 cases, it was not possible to acquire satisfactory uterine artery waveforms, secondary to technical difficulties associated with imaging this vessel in late gestation. The median uterine artery PI was 0.70 (range 0.26 – 2.14) with a 10^{th} centile value of 0.47 and a 90^{th} centile value of 1.03. Uterine artery PI had a non-normal distribution in the study population (Skewness = 1.53, Kurtosis = 5.24, D'agostino-Pearson p = <0.001).

No significant variation in uterine artery PI was observed between the different mode of delivery groups (Table 34).

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS FTP	Kruskal Wallis
Number of Patients	460	47	90	185	70	68	
Uterine artery PI	0.70 (0.26 – 2.14)	0.78 (0.35 – 1.64)	0.70 (0.41 – 1.29)	0.70 (0.26 – 2.13)	0.71 (0.37 – 2.14)	0.66 (0.30 – 1.37)	0.16

Table 36. Uterine artery PI according to mode of delivery group

Using a Dunn's multiple comparison test, the uterine artery PI of each mode of delivery group was compared to all others (Table 35). No significant differences were identified.

	Difference in rank sum	p = <0.05
Emergency LSCS FD vs. Instrumental FD	25.27	No
Emergency LSCS FD vs. SVD	26.25	No
Emergency LSCS FD vs. Instrumental FTP	35.96	No
Emergency LSCS FD vs. Emergency LSCS other	61.57	No
Instrumental FD vs. SVD	0.9785	No
Instrumental FD vs. Instrumental FTP	10.69	No
Instrumental FD vs. Emergency LSCS other	36.31	No
SVD vs. Instrumental FTP	9.713	No
SVD vs. Emergency LSCS other	35.33	No
Instrumental FTP vs. Emergency LSCS other	25.61	No

Table 37. Dunn's multiple comparison test – uterine artery PI

As no significant variation in uterine artery PI was observed between the different mode of delivery groups, this parameter did not undergo further statistical analysis.

Amniotic Fluid Volume

The amniotic fluid index was recorded from all 604 cases in the study population. The median AFI was 8.7 (range 0.1 – 32.0) with a 10th centile value of 4.6 and a 90th centile value of 15.3. Amniotic fluid index had a non-normal distribution within the study population (Skewness = 0.96, Kurtosis = 2.13, D'agostino-Pearson p = <0.001). Deepest vertical pool was also recorded from all 604 cases. The median DVP was 3.9 (range 0.1 – 12.6), with a 10th centile value of 2.2 and a 90th centile value of 6.7. The DVP had a non-normal distribution in the study population (Skewness = 0.82, Kurtosis = 1.11. D'agostino-Pearson p = <0.001).

Whilst the lowest AFI and DVP were found in the group of fetuses subsequently delivered by emergency caesarean delivery for presumed fetal compromise, no significant difference in either AFI or DVP were observed between the different mode of delivery groups (Table 36).

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	604	69	110	238	96	91	
AFI	8.7 (0.1 – 32.0)	7.8 (0.1 – 24.0)	8.7 0.1 – 23.0)	9.0 (1.0 – 26.9)	8.9 (1.5 – 32.0)	8.6 (1.0 – 19.5)	0.06
DVP	3.9 (0.1 – 12.6)	3.5 (0.0 – 9.3)	3.8 (0.0 – 8.7)	3.9 (1.0 – 11.1)	4.2 (1.5 – 12.6)	4.0 (1.0 – 8.8)	0.06

Table 38. AFI and DVP according to mode of delivery group

Using Dunn's multiple comparison test, the AFI and DVP of each mode of delivery group was compared to all others (Table 37). The AFI and DVP of fetuses subsequently delivered by emergency caesarean for presumed fetal compromise was significantly different to that of fetuses born by SVD.

	Difference in rank sum - AFI	AFI p = <0.05	Difference in rank sum - DVP	DVP p = <0.05
Emergency LSCS FD vs. Instrumental FD	-46.54	No	-51.43	No
Emergency LSCS FD vs. SVD	-69.88	Yes	-69.38	Yes
Emergency LSCS FD vs. Instrumental FTP	-63.23	No	-67.00	No
Emergency LSCS FD vs. Emergency LSCS other	-52.13	No	-62.35	No
Instrumental FD vs. SVD	-23.34	No	-17.95	No
Instrumental FD vs. Instrumental FTP	-16.69	No	-15.57	No
Instrumental FD vs. Emergency LSCS other	-5.597	No	-10.92	No
SVD vs. Instrumental FTP	6.644	No	2.382	No
SVD vs. Emergency LSCS other	17.74	No	7.028	No
Instrumental FTP vs. Emergency LSCS other	11.10	No	4.646	No

Table 39. Dunn's multiple comparison test – AFI and DVP

As only limited variation in AFI or DVP was observed between the different mode of delivery groups, these parameters did not undergo further statistical analysis.

Estimated fetal Weight

An estimated fetal weight (EFW) was calculated from fetal biometry for all 604 cases in the study population. The mean EFW was 3547g (range 2136g – 5037g) with a 10th centile value of 2982g and a 90th centile value of 4130g. Estimated fetal weight had a normal distribution in the study population (Skewness = 0.06, Kurtosis = 0.16, D'agostino-Pearson p = 0.58).

Estimated fetal weights were compared between the different mode of delivery groups. Fetuses born by emergency caesarean section for presumed fetal compromise had the lowest EFW, while those born by emergency caesarean for "other" indication had the largest EFW, although this finding was not significant when compared using one-way ANOVA (Table 38).

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	ANOVA
Number of Patients	604	69	110	238	96	91	
EFW (g)	3547 (2136 – 5037)	3469 (2382 – 4713)	3471 (2136 – 4532)	3504 (2433 – 4779)	3642 (2409 – 5037)	3711 (2397 – 4706)	0.89

Table 40. Estimated fetal weight according to mode of delivery

Using Bonferroni's multiple comparisons test, the EFW of each mode of delivery group was compared to all others (Table 39). Fetuses born by emergency caesarean section for an indication other than fetal compromise had a significantly larger EFW than those born by emergency caesarean for presumed fetal compromise, instrumental for presumed fetal compromise, or SVD.

	Difference in mean EFW	95% CI of means	p = <0.05
Emergency LSCS FD vs. Instrumental FD	-1.356	-196.4 to 193.7	No
Emergency LSCS FD vs. SVD	-35.10	-208.8 to 138.5	No
Emergency LSCS FD vs. Instrumental FTP	-172.6	-373.0 to 27.88	No
Emergency LSCS FD vs. Emergency LSCS other	-242.0	-444.8 to -39.30	Yes
Instrumental FD vs. SVD	-33.75	-180.2 to 112.7	No
Instrumental FD vs. Instrumental FTP	-171.2	-348.6 to 6.177	No
Instrumental FD vs. Emergency LSCS other	-240.7	-420.7 to -60.72	Yes
SVD vs. Instrumental FTP	-137.5	-291.0 to 16.09	No
SVD vs. Emergency LSCS other	-206.9	-363.5 to -50.41	Yes
Instrumental FTP vs. Emergency LSCS other	-69.48	-255.3 to 116.3	No

Table 41. Bonferroni multiple comparisons test – Estimated Fetal Weight

As only limited variation in EFW was observed, no further analysis was undertaken for this parameter.

Receiver-operator-characteristic Curve analysis

Variation in UA PI, MCA PI, the C/U ratio and corrected UV flow were all associated with subsequent differences in the incidence of fetal compromise in labour. The performance of these markers can be compared using ROC curves (Figure 22).

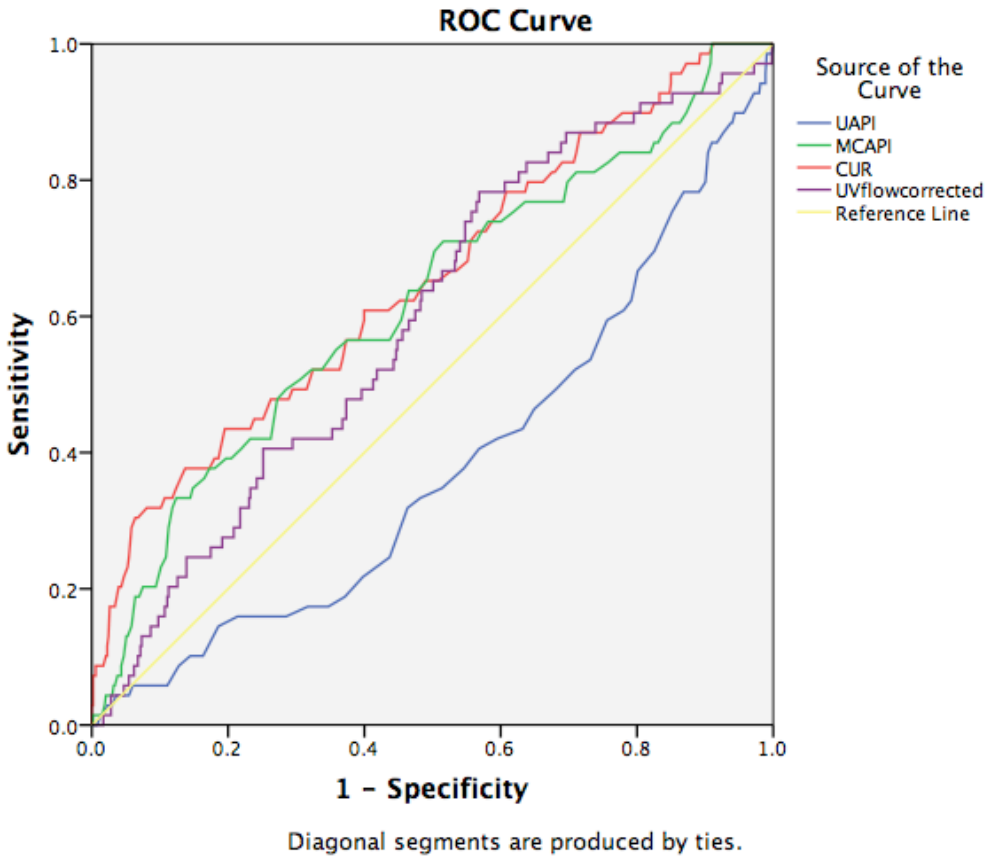


Figure 22. ROC curve comparison

The highest AUC was found for the C/U ratio (0.67, 95% CI 0.58 – 0.74), compared to the MCA PI (0.63, 95% CI 0.55 – 0.71), the UA PI (0.61, 95% CI 0.55 – 068) and the corrected UV flow rate (0.60, 95% CI 0.53 – 0.66). Whilst all were significant predictors of subsequent caesarean delivery for presumed fetal compromise (p = <0.05), the predictive performance of all was limited. When compared to one another, no significant difference in the AUC was identified between the different predictors.

Regression analyses

Regression analysis was performed to correct for any potential confounding variables, and to determine which of the ultrasound parameters was independently predictive of caesarean delivery for presumed fetal compromise. Potential confounding variables included maternal demographic variables as well as the ultrasound parameters themselves. Binary logistic regression analysis was conducted, with the dependent variable being Caesarean section for presumed fetal compromise. Of the maternal demographic characteristics, maternal age, gestation, and parity were considered potential confounding factors. When examining the influence of the C/U ratio on the dependent variable, expert statistical advice was sought and confirmed it was not possible to adjust for both the UA PI and MCA PI, as being components of the C/U ratio they are not independent of it. All other ultrasound parameters, including estimated fetal weight, UV flow, and AFI were included in the logistic regression model. Within this model, the C/U ratio remained predictive of caesarean section for presumed fetal compromise ($p = 0.001$, odds ratio 0.29 95% CI 0.14 – 0.60).

The analysis was repeated including the MCA PI and UA PI, but without the C/U ratio. After adjustment for the other potential confounding variables the UA PI and the MCA PI remained significant predictors of caesarean delivery for presumed fetal compromise ($p = 0.005$, odds ratio 13.68 95% CI 2.24 – 83.37 and $p = 0.01$, 95% CI 0.25 95% CI 0.08 – 0.75).

The analysis was also repeated including the C/U ratio and UA PI (alongside the other previously mentioned variables) and including the C/U ratio and MCA PI, to determine if the C/U ratio offered additional predictive value on top of its constituent components. In both cases the C/U ratio remained independently predictive of Caesarean delivery for presumed fetal compromise ($p = 0.02$, odds ratio 0.35 95% CI 0.15 – 0.84 and $p = 0.01$, odds ratio 0.26 95% CI 0.09 – 0.74 respectively)

Multinomial regression analysis was also conducted with mode of delivery as the dependent variable. Each mode of delivery group was compared to the SVD group, and the same potential confounders were included in the regression model. The C/U ratio remained a significant predictor of caesarean delivery for fetal compromise ($p = 0.001$, odds ratio 0.27 95% CI 0.12 – 0.61).

Intra-partum and Neonatal Outcomes

Intra-partum outcomes assessed included the incidence of CTG abnormalities (classified according to NICE criteria) and the presence or absence of meconium stained liquor. Neonatal outcomes investigated included Apgar scores, umbilical artery pH and base excess at delivery, and the incidence of neonatal unit admission and neonatal encephalopathy. A composite neonatal outcome score was also calculated.

Intra-partum monitoring

All cases had intra-partum monitoring either intermittent, or continuous. Cases with normal intermittent monitoring (not requiring the commencement of continuous monitoring) and those with normal continuous monitoring throughout labour were, for the purposes of data analysis, amalgamated to form one group.

Cardiotocograph (CTG) recordings were defined as normal, suspicious, or pathological on the basis of National Institute for Health and Clinical Excellence (NICE)[332] criteria for CTG interpretation. These national guidelines are used to improve consistency in CTG interpretation, and are similar to those of the American Congress of Obstetricians and Gynecologists (ACOG)[98]. Within the study population 211 cases had fetal heart rate (FHR) patterns classified as normal, 274 classified as suspicious, and 119 classified as pathological. Cases were grouped according to these classifications and the ultrasound parameters compared between those with normal, suspicious, and pathological (FHR) patterns (Table 40).

	FHR – Normal	FHR – suspicious	FHR - pathological	Kruskal-Wallis/ANOVA p=
UA PI	0.76 (0.46 - 1.42)	0.79 (0.51 – 1.21)	0.82 (0.53 – 1.53)	0.02
MCA PI	1.41 (0.72 – 2.29)	1.34 (0.70 – 2.32)	1.29 (0.68 – 1.89)	<0.001
C/U ratio	1.83 (1.03 – 3.29)	1.73 (0.81 – 2.88)	1.58 (0.59 – 2.77)	<0.001
UV flow rate (ml/min)	219.7 (34.6 – 577.1)	210.4 (35.1 – 452.4)	195.2 (17.9 – 426.6)	0.001
Corrected UV flow rate (ml/min/kg)	60.6 (11.0 – 139.0)	60.6 (10.1 – 124.8)	58.0 (4.5 – 130.6)	0.12
Uterine artery PI	0.70 (0.26 – 1.50)	0.70 (0.30 – 2.14)	0.74 (0.41 – 1.19)	0.30
AFI	9.2 (1.5 – 23.0)	8.4 (0.1 – 23.0)	8.2 (0.1 – 23.0)	0.009
DVP	4.2 (1.2 – 11.1)	3.9 (0.1 – 12.6)	3.6 (0.1 – 8.4)	0.04
EFW (g)	3619 (2409 - 5037)	3528 (2397 - 4779)	3464 (2136 - 4713)	0.02

Table 42. Ultrasound parameters according to Intra-partum FHR classification

The UA PI varied significantly between the FHR classification groups. Those fetuses with pathological heart rate patterns during labour had the highest UA PI. Dunn's multiple comparison test confirmed that only the difference between the "normal" and "pathological" groups reached statistical significance. The MCA PI was also found to have significant variation between the different FHR classification groups. Fetuses with pathological heart rate patterns during labour had the lowest MCA PI. Dunn's test of multiple comparisons confirmed that the MCA PI in fetuses with normal intra-partum monitoring differed significantly from those with suspicious and pathological heart rate patterns. Similarly, there was significant variation in the C/U ratio between the different FHR classification groups. Dunn's multiple comparison test confirmed that the C/U ratio of each group differed significantly from all other groups.

Umbilical venous flow rate also varied significantly between the FHR classification groups. Fetuses with pathological heart rate patterns during labour had the lowest UV flow rate, however, when Dunn's multiple comparisons test was conducted, the UV flow rate in fetuses with normal intra-partum monitoring was only significantly different to those with pathological fetal heart rate patterns. Whilst corrected UV flow rates were lowest in fetuses with pathological heart rate patterns during labour, this finding was not statistically significant. Similarly, no significant variation in uterine artery PI was observed between FHR classification groups.

Significant variation in AFI was observed between the FHR classification groups. Dunn's multiple comparison test confirmed that the AFI of fetuses with normal FHR patterns was significantly different to that of fetuses with both suspicious and pathological heart rate patterns. Whilst significant variation in DVP was observed between the FHR classification groups when tested using the Kruskal-Wallis test, no significant differences were found using Dunn's multiple comparisons test.

Significant variation in EFW was observed between the different intra-partum monitoring groups. Fetuses with pathological heart rate patterns during labour had the lowest EFW. Dunn's multiple comparisons test confirmed that the EFW of these fetuses was significantly smaller (although >10th centile for gestation) than those with normal intra-partum monitoring.

Maternal demographics were compared between the different intra-partum monitoring groups (Table 41). Significant variation in the proportion of nulliparous women and the gestational age was observed between the intra-partum monitoring groups. Cases with pathological FHR patterns had the greatest proportion of nulliparous women and the latest gestation, although the absolute difference in gestation between the groups was small.

	Overall	CTG – Normal	CTG – Suspicious	CTG - Pathological	ANOVA/χ^2
Number of Patients	604	211	274	119	
% Nulliparous	75.3% (455/604)	64.5% (136/211)	76.6% (210/274)	91.6% (109/119)	0.02
Mean Maternal Age (Years)	32.3 (16 – 47)	32.8 (18 – 47)	32.1 (16 – 45)	32.2 (23 – 44)	0.50
Median BMI (Kg/m^2)	24.0 (16 – 42)	24.0 (17.0 – 41.0)	24.0 (16.0 – 40.0)	23.7 (17.0 – 42.0)	0.35
Median gestation (weeks)	41.0 (37.0 – 42.0)	40.7 (37.0 – 42.0)	41.0 (37.0 – 42.0)	41.3 (37.0 – 42.0)	0.04
Ethnicity (%)					
Caucasian	67.7% (409/604)	68.7% (145/211)	68.6% (188/274)	63.9% (76/119)	0.85
Asian	17.4% (105/604)	15.6% (33/211)	15.3% (42/274)	25.2% (30/119)	0.07
Afro-Caribbean	10.3% (62/604)	11.8% (25/211)	9.6% (27/274)	8.4% (10/119)	0.62
Other	4.6% (28/604)	3.8% (8/211)	6.2% (17/274)	2.5% (3/119)	0.23
Mode of onset of labour (%)					
Induction	80.3% (485/604)	82.0% (173/211)	79.6% (218/274)	79.0% (94/119)	0.94
Spontaneous	19.7% (119/604)	18.0%(38/211)	20.4% (56/274)	21.0% (25/119)	0.78

Table 43. Maternal demographics according to intra-partum FHR classification.

Passage of Meconium

Liquor composition was recorded for all 604 cases in the study population. Meconium stained liquor occurred in 12.6% (76/604) of cases and clear liquor in 87.4% (528/604) of cases. Between cases with clear liquor and those with meconium stained liquor, significant variation was observed in only the MCA PI (Table 42). Cases with meconium stained liquor had a significantly lower MCA PI than those with clear liquor.

	Clear liquor	Meconium stained liquor	p=
UA PI	0.79 (0.46 – 1.53)	0.77 (0.52 – 1.16)	0.83
MCA PI	1.36 (0.69 – 2.29)	1.26 (0.68 – 2.32)	0.003
C/U ratio	1.76 (0.59 – 3.29)	1.74 (0.83 – 2.78)	0.08
UV flow (ml/min)	207.8 (34.6 – 577.1)	216.7 (17.9 – 377.6)	0.31
Corrected UV flow (ml/min/kg)	60.0 (10.1 – 139.0)	61.8 (4.5 – 130.6)	0.54
Uterine artery PI	0.70 (0.26 – 2.14)	0.70 (0.39 – 1.64)	0.98
AFI	8.7 (0.1 – 26.9)	8.6 (0.9 – 32.0)	0.84
DVP	3.9 (0.1 – 11.1)	4.2 (0.9 – 12.6)	0.73
EFW (g)	3540 (2136 – 5037)	3601 (2489 – 4614)	0.20

Table 44. Ultrasound parameters according to liquor status

Maternal demographics were also compared between the two groups. The meconium stained liquor group had a significantly later gestation than the clear liquor group. Significant differences were also observed in the proportion of cases with spontaneous onset of labour, and in the proportion of women with 'other' ethnicity (Table 43).

	Overall	Clear Liquor	Meconium stained liquor	ANOVA/χ^2
Number of Patients	604	528	76	
% Nulliparous	75.3% (455/604)	73.3% (387/528)	89.5% (68/76)	0.13
Mean Maternal Age (Years)	32.3 (16 – 47)	32.4 (16.0 – 47.0)	32.1 (22.0 – 44.0)	0.89
Median BMI (Kg/m^2)	24.0 (16 – 42)	24.0 (16.0 – 42.0)	24.0 (19.0 – 41.0)	0.85
Median gestation (weeks)	41.0 (37.0 – 42.0)	40.9 (37.0 – 42.0)	41.4 (38.0 – 42.0)	0.004
Ethnicity (%)				
Caucasian	67.7% (409/604)	67.0% (354/528)	72.4% (55/76)	0.60
Asian	17.4% (105/604)	17.2% (91/528)	18.4% (14/76)	0.74
Afro-Caribbean	10.3% (62/604)	10.4% (55/528)	9.2% (7/76)	0.76
Other	4.6% (28/604)	5.3% (28/528)	0.0% (0/76)	0.04
Mode of onset of labour (%)				
Induction	80.3% (485/604)	82.2% (434/528)	67.1% (51/76)	0.17
Spontaneous	19.7% (119/604)	17.8% (94/528)	32.9% (25/76)	0.006

Table 45. Maternal demographics and mode of onset of labour according to liquor group

The incidence of adverse intra-partum outcomes (suspicious/pathological FHR monitoring and meconium stained liquor) were then compared between the centile groups of each ultrasound parameter.

Relationship between intra-partum outcomes and umbilical artery PI

No significant variation in the incidence of pathological or suspicious FHR patterns or the incidence of meconium stained liquor was observed between the different UA PI centile groups (Table 44).

	Overall	UA PI <10th Centile 50	UA PI 10th-90th Centile 495	UA PI>90th Centile 59	X^2 p=	Relative risk <10th centile vs. >90th centile
FHR monitoring - Pathological	19.7% (119/604)	12.0% (6/50)	20.8% (103/495)	16.9% (10/59)	0.36	0.71 95% CI 0.28 – 1.81
FHR monitoring - Suspicious	45.4% (274/604)	54.0% (27/50)	44.2%(219/495)	47.5% (28/59)	0.60	1.14 95% CI 0.79 – 1.65)
Meconium stained liquor	12.6% (76/604)	16.0% (8/50)	11.7% (58/495)	16.9% (10/59)	0.44	0.94 95% CI 0.40 – 2.21

Table 46. Comparison of intra-partum outcomes in each UA PI centile group

Relationship between intra-partum outcomes and Middle Cerebral Artery PI

Fetuses with the lowest MCA PI were significantly more likely to subsequently develop a pathological FHR pattern during labour, with a relative risk of five when compared to fetuses with the highest MCA PI values (Table 45). No significant variation in the incidence of "suspicious" FHR patterns or that of meconium stained liquor were observed between the MCA PI centile groups.

	Overall	MCA PI <10th Centile 54	MCA PI 10th-90th Centile 496	MCA PI >90th Centile 54	X^2 p=	Relative risk <10th centile vs. >90th centile
FHR monitoring - Pathological	19.7% (119/604)	27.8% (15/54)	20.4% (101/496)	5.6% (3/54)	0.02	5.0 95% CI 1.54 – 16.29
FHR monitoring - Suspicious	45.4% (274/604)	50.0% (27/54)	45.2% (224/496)	42.6% (23/54)	0.84	1.17 95% CI 0.78 – 1.77
Meconium stained liquor	12.6% (76/604)	16.7% (9/54)	12.3% (61/496)	11.1% (6/54)	0.66	1.50 95% CI 0.57 – 3.92

Table 47. Comparison of intra-partum outcomes in each MCA PI centile group

Relationship between intra-partum outcomes and cerebro-umbilical ratio

Significant variation in the incidence of pathological intra-partum monitoring was observed between the C/U ratio centile groups. Fetuses with the lowest C/U ratios were four times more likely to develop pathological FHR patterns during labour than those with the highest C/U ratios (Table 46).

	Overall	C/U ratio <10th Centile 58	C/U ratio 10th-90th Centile 488	C/U ratio >90th Centile 58	X^2 p=	Relative risk <10th centile vs. >90th centile
FHR monitoring - Pathological	19.7% (119/604)	37.9% (22/58)	18.9% (92/488)	8.6% (5/58)	0.001	4.4 95% CI 1.79 – 10.83
FHR monitoring - Suspicious	45.4% (274/604)	46.6% (27/58)	45.1% (220/488)	46.6% (27/58)	0.98	1.00 95% CI 0.68- 1.48
Meconium stained liquor	12.6% (76/604)	22.4% (13/58)	11.9% (58/488)	8.6% (5/58)	0.07	2.60 95% CI 0.99 – 6.82

Table 48. Comparison of intra-partum outcomes in each C/U ratio centile group

No significant variations in the intra-partum outcome measures were observed between the centile groups for UV flow, Corrected UV flow, amniotic fluid index, deepest vertical pool, or estimated fetal weight.

Intra-partum outcomes summary

There was significant variation in UA PI, UV flow rate, AFI, DVP, and EFW between the different FHR classification groups, but this variation was not sufficient to be predictive of subsequent pathological FHR patterns. The MCA PI and C/U ratio were the only parameters found to be predictive of subsequent pathological FHR patterns during labour.

MCA PI was the only ultrasound parameter found to vary significantly between cases with clear liquor, and those with meconium stained liquor. A significant difference in the incidence of meconium stained liquor was not found between the centile groups of any of the ultrasound parameters.

Neonatal outcomes

Birthweight and birthweight centile (adjusted for gestation) were recorded for all 604 cases in the study population. The mean birthweight was 3530g (1780g – 5026g), with a 10th centile value of 2690g and a 90th centile value of 4125g. Birthweight was normally distributed within the study population (Skewness = 0.10, Kurtosis = 0.21, D'agostino-Pearson p = 0.32). Other neonatal outcomes including the incidence of an Apgar score <7 at one and five minutes, the incidence of umbilical artery pH <7.20, umbilical artery base excess <-8.0, neonatal unit admission, and neonatal encephalopathy were all recorded. A composite neonatal outcome score was also calculated.

Neonatal outcome variables were compared between the different mode of delivery groups (Table 47). Significant variation in birthweight and birthweight centile was found between the groups. Those infants born by emergency caesarean for presumed fetal compromise had the lowest birthweight and birthweight centile. Bonferroni multiple comparisons test confirmed that infants born by emergency caesarean section 'other' were significantly larger than infants in all other mode of delivery groups. When birthweight centile was analysed using the multiple comparisons test, infants born by emergency caesarean for presumed fetal compromise had a significantly lower birthweight centile than either the instrumental for prolonged 2nd stage or caesarean 'other' groups.

There was also significant variation in the incidence of an Apgar score <7 at 1 minutes, although this variation was no longer present amongst 5 minute Apgar scores. The incidence of low Apgar scores was highest amongst those infants born by instrumental delivery for presumed fetal compromise, and those born by instrumental delivery for a prolonged 2nd stage. Similarly, infants born by instrumental delivery for presumed fetal compromise had the highest incidence of acidosis at delivery, and the highest incidence of a significant base deficit.

There was no significant variation in the incidence of neonatal unit admission between the different mode of delivery groups. No cases of neonatal encephalopathy occurred within the study population.

The composite neonatal outcome scores had significant variation between the mode of delivery groups, with those infants born by instrumental delivery for presumed fetal

compromise having the highest scores. Dunn's multiple comparison test, confirmed that this group had significantly higher scores than all other mode of delivery groups, except the SVD group.

	Overall	Emergency caesarean Fetal compromise	Instrumental Fetal Compromise	SVD	Instrumental Prolonged 2nd stage	Emergency caesarean other	ANOVA/ X^2 p=
Mean Birthweight (g)	3530 (1780 – 5026)	3426 (2478 – 4906)	3469 (1780 – 4940)	3495 (2520 – 4480)	3618 (2390 – 5026)	3682 (2690 – 4506)	<0.001
Median Birthweight centile	53.5 (1 – 100)	44.39 (1 – 100)	49.38 (1 – 100)	52.01 (2 – 99)	58.27 (2 – 100)	62.69 (5 – 99)	<0.001
Incidence Apgar <7 at 1 min	7.5% (45/604)	10.1% (7/69)	14.5% (16/110)	3.8% (9/238)	11.5% (11/96)	2.2% (2/91)	0.001
Incidence Apgar <7 at 5 min	1.0% (6/604)	1.4% (1/69)	0.9% (1/110)	0.4% (1/238)	2.0% (2/96)	1.1% (1/91)	0.72
Incidence Cord arterial pH < 7.20	31.3% (189/604)	26.1% (18/69)	47.3% (52/110)	35.3% (84/238)	25.0% (24/96)	12.1% (11/91)	<0.001
Incidence Base Excess < -8	24.2% (146/604)	11.6% (8/69)	33.6% (37/110)	30.7% (73/238)	22.9% (22/96)	6.6% (6/91)	<0.001
Incidence of neonatal unit admission	1.5% (9/604)	2.9% (2/69)	2.7% (3/110)	0.8% (2/238)	1.0% (1/96)	1.1% (1/91)	0.57
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/69)	0% (0/110)	0% (0/238)	0% (0/96)	0% (0/91)	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.64 (0 – 5)	1.2 (0 – 5)	0.85 (0 – 7)	0.70 (0 – 5)	0.31 (0 – 5)	<0.001

N.b Composite Neonatal outcome scored as follows

1. **Apgar - >7 @ 1 min = 0, <7 @ 1 min =1, <7 @5 min = 2**
2. **Cord arterial pH - >7.20 = 0, <7.20 = 1, <7.10 = 2, < 7.00 = 3**
3. **Base excess - >-8 = 0, <-8 and >-12 = 1, <-12 = 2**
4. **NNU admission - No = 0, Yes = 1**

Table 49. Comparison of neonatal outcome variables between mode of delivery groups

The neonatal outcome variables were then compared between the centile groups of each ultrasound parameter.

Relationship between neonatal outcome variables and umbilical artery PI (Table 48)

Both birthweight and birthweight centile varied significantly between the UA PI centile groups. The highest UA PI values corresponded to the lowest birthweight and birthweight centile. Multiple comparison tests confirmed that the variation in birthweight was significant between all groups, whilst birthweight centile was significantly lower in cases with the highest UA PI values. No other neonatal outcome variables varied significantly between the UA PI centile groups.

	Overall	**UA PI <10th Centile** 50	**UA PI 10th-90th Centile** 495	**UA PI>90th Centile** 59	**ANOVA/ X^2 p=**	**Relative risk <10th centile vs. >90th centile**
Mean Birthweight (g)	3530 (1780 – 5026)	3723 (2360 – 4550)	3549 (2390 – 5026)	3204 (1780 – 4498)	<0.001	n/a
Median Birthweight centile	53.5 (1 – 100)	67.0 (5 – 100)	55.0 (1 – 100)	31.0 (1 – 100)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.5% (45/604)	6.0% (3/50)	8.1% (40/495)	3.4% (2/59)	0.43	1.77 95% CI 0.31 – 10.18
Incidence Apgar <7 at 5 min	1.0% (6/604)	0% (0/50)	1.2% (6/495)	0% (0/59)	0.52	n/a
Incidence Cord arterial pH < 7.20	31.3%(189/604)	26.0%(13/50)	31.5%(156/495)	33.9%(20/59)	0.75	0.77 95% CI 0.43 – 1.38
Incidence Base Excess < -8	24.2%(146/604)	20.0%(10/50)	24.0%(119/495)	28.8%(17/59)	0.64	0.69 95% CI 0.35 – 1.38
Incidence of neonatal unit admission	1.5% (9/604)	0% (0/50)	1.4% (7/495)	3.4% (2/59)	0.34	n/a
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/50)	0% (0/495)	0% (0/59)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.54 (0 – 3)	0.79 (0 – 5)	0.90 (0 – 7)	0.68	n/a

Table 50. Comparison of neonatal outcome variables between UA PI centile groups

Relationship between neonatal outcome variables and middle cerebral artery PI (Table 49)

Only the incidence of neonatal unit admission varied significantly between the MCA PI centile groups, with the highest incidence of neonatal unit admission found in cases with the highest MCA PI. However, these cases were not at significantly increased risk of neonatal unit admission when compared to those with the lowest MCA PI.

	Overall	MCA PI <10th Centile 54	MCA PI 10th-90th Centile 496	MCA PI>90th Centile 54	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3530 1780 – 5026)	3577 (2630 – 4906)	3526 (1780 – 5026)	3520 (2680 – 4498)	0.74	n/a
Median Birthweight centile	53.5 (1 – 100)	52.0 (3 – 100)	54.0 (1 – 100)	53.0 (5 – 99)	0.89	n/a
Incidence Apgar <7 at 1 min	7.5% (45/604)	3.7% (2/54)	7.3% (36/496)	13.0% (7/54)	0.20	0.29 95% CI 0.06 – 1.31
Incidence Apgar <7 at 5 min	1.0% (6/604)	1.9% (1/54)	0.8% (4/496)	1.9% (1/54)	0.62	1.00 95% CI 0.06 – 15.58
Incidence Cord arterial pH < 7.20	31.3% (189/604)	27.8% (15/54)	31.0% (154/496)	37.0% (20/54)	0.67	0.75 95% CI 0.43 – 1.30
Incidence Base Excess < -8	24.2% (146/604)	24.1% (13/54)	24.0% (119/496)	25.9% (14/54)	0.96	0.93 95% CI 0.48 – 1.79
Incidence of neonatal unit admission	1.5% (9/604)	1.9% (1/54)	1.0% (5/496)	5.6% (3/54)	0.03	0.33 95% CI 0.04 – 3.10
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/54)	0% (0/496)	0% (0/54)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.78 (0 – 5)	0.76 (0 – 5)	0.98 (0 – 7)	0.35	n/a

Table 51. Comparison of neonatal outcome variables between MCA PI centile groups

Relationship between neonatal outcome variables and the cerebro-umbilical ratio (Table 50)

Only birthweight centile varied significantly between the C/U ratio centile groups. Cases with the highest C/U ratios had the highest mean birthweight centile. Dunn's multiple comparisons test confirmed that cases with a C/U ratio <10th centile had significantly lower birthweight centile than those with a C/U ratio >90th centile.

	Overall	C/U ratio <10th Centile 58	C/U ratio 10th-90th Centile 488	C/U ratio >90th Centile 58	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3530 (1780 – 5026)	3443 (1780 – 4906)	3530 (2390 – 5026)	3614 (2360 – 4440)	0.14	n/a
Median Birthweight centile	53.5 (1 – 100)	45.0 (1 – 100)	54.0 (1 – 100)	58.0 (5 – 99)	0.02	n/a
Incidence Apgar <7 at 1 min	7.5% (45/604)	6.9% (4/58)	7.0% (34/488)	12.1% (7/58)	0.40	0.57 95% CI 0.18 – 1.85
Incidence Apgar <7 at 5 min	1.0% (6/604)	1.7% (1/58)	0.8% (4/488)	1.7% (1/58)	0.68	1.00 95% CI 0.06 – 15.61
Incidence Cord arterial pH < 7.20	31.3% (189/604)	34.5% (20/58)	30.9% (151/488)	31.0% (18/58)	0.90	1.11 95% CI 0.66 – 1.87
Incidence Base Excess < -8	24.2% (146/604)	22.4% (13/58)	24.0% (117/488)	27.6% (16/58)	0.83	0.81 95% CI 0.43 – 1.53
Incidence of neonatal unit admission	1.5% (9/604)	3.4% (2/58)	1.0% (5/488)	3.4% (2/58)	0.16	1.00 95% CI 0.15 – 6.86
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/58)	0% (0/488)	0% (0/58)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.91 (0 – 5)	0.75 (0 – 7)	0.88 (0 – 5)	0.46	n/a

Table 52. Comparison of neonatal outcome variables between C/U ratio centile groups

Relationship between neonatal outcome variables and umbilical venous flow rate (Table 51)

Significant variation was observed in both birthweight and birthweight centile, between the different UV flow rate centile groups. The largest birthweight and greatest birthweight centile were both found amongst cases with a UV flow rate >90th centile. Multiple comparisons tests confirmed that all three UV flow rate centile groups were significantly different from one another. No significant variation was observed between the other individual neonatal outcome variables.

The composite neonatal outcome score did have significant variation between the UV flow rate centile groups, with cases with a UV flow rate <10th centile having the lowest composite score. Multiple comparison testing confirmed these cases had significantly lower composite neonatal outcomes scores than either of the other UV flow rate centile groups.

	Overall	UV flow rate <10th Centile 60	UV flow rate 10th-90th Centile 482	UV flow rate >90th Centile 60	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3530 (1780 – 5026)	3224 (1780 – 4200)	3518 (2360 – 5026)	3935 (2610 – 4900)	<0.001	n/a
Median Birthweight centile	53.5 (1 – 100)	27.5 (1 – 95)	52.0 (1 – 100)	86.0 (7 – 100)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.5% (45/602)	3.3% (2/60)	7.9% (38/482)	8.3% (5/60)	0.46	0.40 95% CI 0.08 – 1.98
Incidence Apgar <7 at 5 min	1.0% (6/602)	0% (0/60)	0.8% (4/482)	3.3% (2/60)	0.13	n/a
Incidence Cord arterial pH < 7.20	31.4% (189/602)	20.0% (12/60)	32.4% (156/482)	35.0% (21/60)	0.24	0.57 95% CI 0.31 – 1.05
Incidence Base Excess < -8	24.3% (146/602)	11.7% (7/60)	25.5% (123/482)	26.7% (16/60)	0.11	0.44 95% CI 0.19 – 0.99
Incidence of neonatal unit admission	1.5% (9/602)	1.7% (1/60)	1.0% (5/482)	5.0% (3/60)	0.06	0.33 95% CI 0.04 – 3.11
Incidence of neonatal encephalopathy	0% (0/602)	0% (0/60)	0% (0/482)	0% (0/60)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.52 (0 – 7)	0.79 (0 – 5)	0.97 (0 – 5)	0.009	n/a

Table 53. Comparison of neonatal outcome variables between UV flow rate centile groups

Relationship between neonatal outcome variables and corrected umbilical venous flow rate (Table 52)

Significant variation in the composite neonatal outcome score was observed between the corrected UV flow rate centile groups. Multiple comparisons tests confirmed that cases with a corrected UV flow rate <10th centile had significantly lower composite neonatal outcomes scores than those with a corrected UV flow rate >90th centile.

	Overall	Corrected UV flow rate <10th Centile 60	Corrected UV flow rate 10th-90th Centile 482	Corrected UV flow rate >90th Centile 60	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3530 (1780 – 5026)	3473 (2620 – 4906)	3544 (1780 – 5026)	3478 (2390 – 4470)	0.35	n/a
Median Birthweight centile	53.5 (1 – 100)	45.0 (3 – 100)	54.0 (1 – 100)	58.5 (1 – 99)	0.27	n/a
Incidence Apgar <7 at 1 min	7.5% (45/602)	5.0% (3/60)	7.7% (37/482)	8.3% (5/60)	0.75	0.60 95% CI 0.15 – 2.40
Incidence Apgar <7 at 5 min	1.0% (6/602)	0% (0/60)	0.8% (4/482)	3.3% (2/60)	0.13	n/a
Incidence Cord arterial pH < 7.20	31.4% (189/602)	23.3% (14/60)	31.5% (152/482)	38.3% (23/60)	0.34	0.61 95% CI 0.35 – 1.07
Incidence Base Excess < -8	24.3% (146/602)	15.0% (9/60)	25.1% (121/482)	26.7% (16/60)	0.30	0.56 95% CI 0.27 – 1.17
Incidence of neonatal unit admission	1.5% (9/602)	1.7% (1/60)	1.0% (5/482)	5.0% (3/60)	0.06	0.33 95% CI 0.04 – 3.11
Incidence of neonatal encephalopathy	0% (0/602)	0% (0/60)	0% (0/482)	0% (0/60)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.55 (0 – 7)	0.78 (0 – 5)	1.00 (0 – 5)	0.04	n/a

Table 54. Comparison of neonatal outcome variables between corrected UV flow rate centile groups

Relationship between neonatal outcome variables and amniotic fluid index (Table 53)

Significant variation in both birthweight and birthweight centile was found between the AFI centile groups, with the largest birthweight and greatest birthweight centile found in cases with an AFI >90th centile. The significant difference between each of the groups was confirmed by multiple comparison testing.

	Overall	**AFI <10th Centile** 59	**AFI 10th-90th Centile** 485	**AFI >90th Centile** 60	**ANOVA/ X^2 p=**	**Relative risk <10th centile vs. >90th centile**
Mean Birthweight (g)	3530 (1780 – 5026)	3397 (2360 – 4906)	3527 (1780 – 5026)	3680 (2660 – 4550)	0.004	n/a
Median Birthweight centile	53.5 (1 – 100)	37.0 (2 – 100)	54.0 (1 – 100)	62.0 (3 – 100)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.5% (45/604)	5.1% (3/59)	7.2% (35/485)	11.7% (7/60)	0.39	0.44 95% CI 0.12 – 1.61
Incidence Apgar <7 at 5 min	1.0% (6/604)	1.7% (1/59)	0.6% (3/485)	3.3% (2/60)	0.12	0.51 95% CI 0.05 – 5.46
Incidence Cord arterial pH < 7.20	31.3% (189/604)	32.2% (19/59)	30.5% (148/485)	36.7% (22/60)	0.72	0.88 95% CI 0.53 – 1.44
Incidence Base Excess < -8	24.2% (146/604)	28.8% (17/59)	22.9% (111/485)	30.0% (18/60)	0.43	0.96 95% CI 0.55 – 1.68
Incidence of neonatal unit admission	1.5% (9/604)	1.7% (1/59)	1.2% (6/485)	3.3% (2/60)	0.45	0.51 95% CI 0.05 – 5.46
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/59)	0% (0/485)	0% (0/60)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.86 (0 – 5)	0.75 (0 – 5)	0.95 (0 – 7)	0.28	n/a

Table 55. Comparison of neonatal outcome variables between AFI centile groups

Relationship between neonatal outcome variables and deepest vertical pool (Table 54)

Significant variation in both birthweight and birthweight centile was found between the DVP centile groups, with the largest birthweight and greatest birthweight centile found in cases with a DVP >90th centile. The significant difference between each of the groups was confirmed by multiple comparison testing.

	Overall	DVP <10th Centile 61	DVP 10th-90th Centile 484	DVP >90th Centile 59	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3530 (1780 – 5026)	3358 (2360 – 4340)	3526 (1780 – 5026)	3737 (2998 – 4550)	<0.001	n/a
Median Birthweight centile	53.5 (1 – 100)	35.0 (2 – 97)	54.0 (1 – 100)	68.0 (18 – 100)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.5% (45/604)	4.9% (3/61)	7.4% (36/484)	10.2% (6/59)	0.58	0.48 95% CI 0.13 – 1.84
Incidence Apgar <7 at 5 min	1.0% (6/604)	1.6% (1/61)	1.0% (5/484)	0% (0/59)	0.66	n/a
Incidence Cord arterial pH < 7.20	31.3% (189/604)	27.9% (17/61)	32.0% (155/484)	28.8% (17/59)	0.81	0.97 95% CI 0.55 – 1.71
Incidence Base Excess < -8	24.2% (146/604)	26.2% (16/61)	23.6% (114/484)	27.1% (16/59)	0.82	0.97 95% CI 0.53 – 1.75
Incidence of neonatal unit admission	1.5% (9/604)	1.6% (1/61)	1.4% (7/484)	1.7% (1/59)	0.98	0.97 95% CI 0.06 – 15.10
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/61)	0% (0/484)	0% (0/59)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.87 (0 – 5)	0.77 (0 – 5)	0.78 (0 – 7)	0.87	n/a

Table 56. Comparison of neonatal outcome variables between DVP centile groups

Influence of fetal weight - Small for gestational age vs. appropriate for gestational age

Following calculation of gestation controlled birthweight centiles for all cases in the study population, 41 infants were identified with a birthweight <10th centile for gestation, who may have been growth restricted. Maternal demographics (Table 55), ultrasound parameters (Table 56), intra-partum outcomes (Table 57 and 58) and neonatal outcomes (Table 59) were compared between the small for gestational age (SGA) group and the appropriate for gestational age (AGA) group.

A significantly higher proportion of women of Asian ethnicity delivered an infant with birthweight <10th centile. No other differences in maternal demographic parameters were observed between the two groups.

	Overall	SGA (Birthweight <10th Centile)	AGA (Birthweight ≥10th Centile)	Mann Whitney/χ^2
Number of Patients	604	41	563	
% Nulliparous	75.3% (455/604)	78.0% (32/41)	75.1% (423/563)	0.84
Mean Maternal Age	32.3 (16 – 47)	33.5 (24 – 46)	32.3 (16 – 47)	0.18
Median BMI	24.0 (16 – 42)	23.0 (17 – 42)	24.0 (16 – 41)	0.18
Ethnicity (%)				
Caucasian	67.7% (409/604)	48.8% (20/41)	69.1% (389/563)	0.13
Asian	17.4% (105/604)	34.1% (14/41)	16.2% (91/563)	0.008
Afro-Caribbean	10.3% (62/604)	9.8% (4/41)	10.9% (58/563)	0.91
Other	4.6% (28/604)	7.3% (3/41)	4.4% (25/563)	0.41
Mode of onset of labour (%)				
Induction	80.3% (485/604)	80.5% (33/41)	79.0% % (452/572)	0.99
Spontaneous	19.7% (119/604)	19.5% (8/41)	19.4% (111/572)	0.98

Table 57. Maternal demographics according to birthweight group

Significant differences in the UA PI, UV flow rate, AFI, DVP and EFW were present between SGA and AGA infants.

Ultrasound Parameters	Overall	SGA (Birthweight <10th Centile)	AGA (Birthweight ≥10th Centile)	Mann Whitney
UA PI	0.79 (0.46 – 1.53)	0.85 (0.51 – 1.53)	0.78 (0.46 – 1.53)	0.004
MCA PI	1.35 (0.68 – 2.32)	1.40 (0.84 – 1.76)	1.34 (0.68 – 2.32)	0.63
C/U ratio	1.76 (0.59 – 3.29)	1.71 (0.90 – 2.55)	1.76 (0.59 – 3.29)	0.07
UV flow rate (ml/min)	210.1 (17.9 – 577.1)	175.1 (89.9 – 340.9)	213.9 (17.9 – 577.1)	<0.001
Corrected UV flow rate (ml/min/kg)	60.2 (4.5 – 139.0)	64.3 (31.2 – 130.6)	59.9 (4.5 – 139)	0.12
Uterine artery PI	0.70 (0.26 – 2.14)	0.71 (0.35 – 1.39)	0.70 (0.26 – 2.14)	0.44
AFI	8.7 (0.1 – 32.0)	7.5 (0.1 – 15.9)	8.7 (0.1 – 32.0)	0.02
DVP	3.9 (0.1 – 12.6)	3.3 (0.1 – 6.1)	3.9 (0.1 – 12.6)	0.03
EFW	3547 (2136 – 5037)	2890 (2136 – 3508)	3595 (2382 – 5037)	<0.001

Table 58. Mean ultrasound parameter values according to birthweight group

No significant difference in mode of delivery outcomes was identified between SGA and AGA infants.

Delivery category	Overall	SGA (Birthweight <10th Centile)	AGA (Birthweight ≥10th Centile)	χ^2
Caesarean section Fetal compromise	11.4% (69/604)	19.5% (8/41)	10.8% (61/563)	0.11
Fetal compromise diagnosed at any time during labour	29.6% (179/604)	41.5% (17/41)	28.8% (162/563)	0.15
SVD	39.4% (238/604)	46.3% (19/41)	38.9% (219/563)	0.46
Vaginal delivery of any kind	73.5% (444/604)	75.6% (31/41)	73.4% (413/563)	0.87
Caesarean section other indication	15.1% (91/604)	4.9% (2/41)	15.8% (89/563)	0.08

Table 59. Mode of delivery outcomes according to birthweight group

No significant difference in intra-partum outcomes was identified between SGA and AGA infants.

	Overall	SGA (Birthweight <10th Centile)	AGA (Birthweight ≥10th Centile)	χ^2
FHR abnormalities - Pathological	19.7% (119/604)	31.7% (13/41)	18.8% (106/563)	0.07
FHR abnormalities - Suspicious	45.4% (274/604)	43.9% (18/41)	45.5% (256/563)	0.89
Meconium stained liquor	12.6% (76/604)	12.2% (5/41)	12.6% (71/563)	0.94

Table 60. Comparison of intra-partum outcomes between SGA and AGA infants.

No significant differences in neonatal outcome variables were identified between SGA and AGA infants.

	Overall	SGA (Birthweight <10th Centile)	AGA (Birthweight ≥10th Centile)	X^2
Incidence Apgar <7 at 1 min	7.5% (45/604)	7.3% (3/41)	7.5% (42/563)	0.96
Incidence Apgar <7 at 5 min	1.0% (6/604)	0% (0/41)	1.1% (6/563)	0.51
Incidence Cord arterial pH < 7.20	31.3% (189/604)	22.0% (9/41)	32.0% (180/563)	0.27
Incidence Base Excess < -8	24.2% (146/604)	14.6% (6/41)	24.9% (140/563)	0.20
Incidence of neonatal unit admission	1.5% (9/604)	0% (0/41)	1.6% (9/563)	0.42
Incidence of neonatal encephalopathy	0% (0/604)	0% (0/41)	0% (0/563)	n/a
Composite neonatal outcome score	0.78 (0 – 7)	0.61 (0 – 5)	0.79 (0 – 7)	0.24

Table 61. Comparison of neonatal outcome variables between SGA and AGA infants.

Accuracy of estimating fetal weight at term

Estimated fetal weight, calculated using Hadlock's formula, was compared to birthweight for each of the 604 cases in the study population. The mean absolute error was 240g (0g – 898g), and the mean absolute percentage error 6.9% (0% – 34.4%). In 75.5% (456/604) EFW was within 10% of birthweight, and within 15% in 91.7% (554/604). The Pearson correlation coefficient between EFW and birthweight was 0.76 ($p = <0.001$).

Discussion

The hypothesis for this chapter was that ultrasound parameters, measured prior to established labour, would be predictive of subsequent intra-partum fetal compromise and adverse neonatal outcomes.

Following recruitment of over 600 women to this research project, it was demonstrated that within a cohort of normal, appropriately grown fetuses, significant variation existed in the resistance indices of the umbilical artery, middle cerebral artery and in the umbilical venous flow rate, and that these variations were able to identify fetuses at both high and low risk of a subsequent diagnosis of fetal compromise in labour, and the need for emergency delivery. Differences in the resistance indices of fetuses with and without subsequent signs of compromise in labour (meconium stained liquor and abnormal fetal heart rate patterns) were also observed.

Maternal demographics and their relationship with mode of delivery

In order to establish whether any maternal characteristics were associated with fetal compromise in labour, and could therefore act as potential confounding factors, cases were grouped according to mode of delivery and maternal characteristics compared within these groups.

Nulliparous women were at significantly increased risk of requiring emergency delivery during labour for presumed fetal compromise. Caesarean section rates are higher in nulliparous than multiparous women[339]. This may be due to shorter labours in multiparous women compared to nulliparous women[340, 341], and higher intra-uterine pressures associated with contractions in the nulliparous uterus[342]. Longer labours, with higher intra-uterine pressures may contribute to the relatively increased rates of caesarean section found in nulliparous women. Significant variation in gestation at onset of labour was also present between the different mode of delivery groups. However, this variation although statistically significant, may not be of clinical significance. The median gestation of the different mode of delivery groups varied from 40.6 weeks in the SVD group, to 41.4 weeks in the emergency caesarean for presumed fetal compromise group. The absolute difference in gestation was therefore small, being only 0.8 weeks. Whilst gestation does influence the ultrasound parameters used in this study, published longitudinal reference ranges[185, 233, 241,

[248] confirm that there is minimal variation over a time period of 0.8 weeks. No other maternal characteristics had significant variation between the mode of delivery groups.

No significant variation in the mode of delivery outcomes was observed between women undergoing induction of labour and those in spontaneous labour. Whilst traditionally associated with increased rates of Caesarean delivery[343], recent systematic reviews have suggested that induction may be actually be associated with a reduction in Caesarean section rate[344]. Data from this study suggests induction of labour, where there is no underlying indication of reduced placental function, does not significantly influence the subsequent mode of delivery.

Although advanced maternal age has been associated with an increased rate of caesarean section for fetal compromise[345], this relationship was not apparent in data from this study. The reported increased relative risk of caesarean section associated with advanced maternal age is small, and the number of cases in this study is likely to be insufficient to identify this relationship. This study also found no relationship between ethnicity and subsequent mode of delivery.

Maternal demographics and their relationship with ultrasound parameters

The MCA PI, C/U ratio, and AFI were all found to be significantly higher in multiparous women when compared to nulliparous women. This finding is interesting as several complications of pregnancy associated with placental dysfunction have also been demonstrated to occur more frequently in nulliparous women. Pre-eclampsia, which has a similar patho-physiology to, and is often associated with fetal growth restriction, has long been known to occur more frequently in nulliparous women[346]. Perturbations in fetal growth are also more common in nulliparous women[347]. Prefumo et al, suggest that the discrepancy in the incidence of conditions associated with placental dysfunction between nulliparous and multiparous women may be associated with improved trophoblastic invasion in multiparous women[348]. However, few studies have compared the Doppler indices of fetal vessels in nulliparous and multiparous women having normal pregnancies. Increased pressure on the fetal head during ultrasound assessment has been reported to artificially reduce MCA end diastolic flow velocities, and thus increase the measured MCA PI[207]. For a given gestation, the fetal head in nulliparous pregnancy is likely to be more deeply engaged within the maternal pelvis than a multiparous counterpart, there is

therefore potential for the associated head compression to artificially reduce MCA end diastolic flow and increase MCA PI. As a result of this possible confounding influence, the difference in MCA PI between nulliparous women and multiparous women may be even greater than that suggested by data from this study.

There is limited evidence regarding the influence of parity on amniotic fluid volumes, but reduced amniotic fluid volumes are associated with placental dysfunction[255]. Redistribution of fetal cardiac output against a background of intrauterine hypoxia results in a relative reduction in renal perfusion, with a consequent reduction in amniotic fluid production. The significantly higher AFI observed in multiparous women in this study is consistent with the suggestion that placental function may be relatively improved in multiparous pregnancy. The findings from this study, suggest that even in normal pregnancies, subtle differences in placental function between nulliparous and multiparous women may exist.

Significant variations in UA PI, UV flow and estimated fetal weight were observed between the different ethnicities within the study population, with women of Asian ethnicity having the lowest EFW, the second lowest umbilical venous flow rates and the highest UA PI. Maternal ethnicity is known to have a significant impact on fetal birthweight[349], and in particular, Asian ethnicity is associated with reduced birthweight compared to Caucasians[350]. Umbilical venous flow has been reported to have a strong correlation with both fetal head and abdominal circumference[226]. The absence of significant variation in corrected umbilical venous flow (corrected for birthweight) between the ethnic groups suggest that the reduced umbilical venous flow rates observed in women of Asian ethnicity (and those in Afro-Caribbean women) are a function of the reduced birthweight in these groups, rather than an independent finding. The higher UA PI found in women of Asian ethnicity may represent subtle variations in placental function, however whilst this finding was statistically significant, the absolute difference in mean UA PI between the ethnicity groups was small (0.04), and therefore unlikely to be of clinical significance.

Correlation between Doppler parameters and subsequent intra-partum fetal compromise

To evaluate the primary outcome (mode of delivery), cases were grouped according to the mode and indication for delivery, and each ultrasound parameter compared between the groups. Cases were also divided into centile groups, based on each ultrasound parameter, and the incidence of delivery outcomes compared between the centile groups. Significant variation between the mode of delivery groups was observed for :

- UA PI/UA EDF
- MCA PI/MCA EDF
- C/U ratio
- UV flow (significant variation was observed in both UV diameter and Tamax)
- corrected UV flow

No significant variation between the mode of delivery groups was observed for

- Uterine artery PI
- AFI
- DVP
- EFW

Umbilical artery Doppler indices

The umbilical artery was one of the first fetal vessels to be investigated using Doppler ultrasound[(351)], and has since become established as a valuable tool in the investigation and management of pregnancies complicated by fetal growth restriction[(352)]. However, relatively few studies have investigated umbilical artery Doppler indices in appropriately grown fetuses from normal pregnancies. A Cochrane review published in 2010 reported that there was insufficient evidence to warrant use of umbilical artery Doppler as a screening test in "low risk" pregnancy[(353)].

Within the study population, UA PI had a non-normal distribution with significant degree of skewness and kurtosis. This distribution is likely to be a result of the inclusion criteria for the study. Pregnancies with known placental dysfunction, where UA PI will be raised, were specifically excluded from the study population. As a result the distribution had a positive skew (towards lower UA PI). The recruitment of 'normal' pregnancies only, has resulted in a

majority of cases having 'normal' UA PI values, and as such a more peaked distribution than would be expected with less stringent inclusion criteria.

The results from this study suggest that there is significant variation in UA PI between fetuses born by different modes of delivery, even within a cohort of appropriately grown fetuses. However, whilst the variation in UA PI is statistically significant, the absolute variation was small, with only 0.10 separating the lowest mean UA PI (emergency caesarean 'other') and the highest UA PI (emergency caesarean for presumed fetal compromise). Furthermore, multiple comparison testing demonstrated that the UA PI was only significantly different between these two groups, with the highest and lowest UA PI values, and the range of UA PI values in each mode of delivery group had significant overlap with one another. These results would appear to be consistent with published reports that UA PI is not a valuable marker in a low risk population[201]. When cases were grouped according to UA PI centiles, whilst no statistically significant findings were observed, the >90th centile UA PI group did have the highest incidence of caesarean delivery for presumed fetal compromise, and the highest incidence of a diagnosis of fetal compromise at any point during labour. Correspondingly, the <10th centile UA PI group had the lowest incidence of both these outcomes. The positive predictive value of an umbilical artery PI >90th centile for emergency caesarean delivery for presumed fetal compromise was only 17%, suggesting that a significant proportion of fetuses with a raised UA PI are still able to tolerate the stresses of labour sufficiently for vaginal delivery to be achieved.

Of note, UA EDF also had significant variation between the mode of delivery groups. Cases with a UA EDF <10th centile and a UA Tamax <10th centile were at a significantly increased risk of requiring emergency caesarean delivery for presumed fetal compromise. These findings demonstrate umbilical artery resistance indices may be predictive of subsequent caesarean delivery for presumed fetal compromise. These indices, due to their dependence on an insonation angle as close to 0 degrees as possible, may be more challenging to acquire in a systematic and reproducible fashion outside of a research setting. It is for this reason that angle independent measures, such as S/D ratio and PI are used predominantly in clinical practice.

Significant variation in UA PI was observed between the different FHR classification groups. Cases with pathological FHR patterns had the highest UA PI, whilst those with normal FHR patterns had the lowest UA PI. Multiple comparison testing confirmed that fetuses with

normal FHR patterns did have a significantly lower UA PI than those with pathological FHR patterns, but that the difference between the suspicious and pathological groups was not significant. UA PI did not vary significantly between those fetuses with meconium stained liquor and those without.

Apart from a difference in the gestation at onset of labour, maternal demographic characteristics did not vary significantly between the three UA PI centile groups. In this cohort of patients, fetuses with a UA PI >90th centile had a significantly earlier gestation (39.9 weeks) than those with a UA PI in the 10th-90th centile (41.0 weeks), or <10th centile group (41.4 weeks). This finding is consistent with that of longitudinal studies of UA PI throughout pregnancy which show a gradual decline with advancing gestation[185]. However, it is unlikely this finding represents a confounding factor as the absolute difference in gestation between the three groups was small (1.5 weeks). The influence of this small difference in gestation is unlikely to result in significant changes in UA PI values, a suggestion supported by the weak relationship between UA PI and gestation in the study population (figure 15). Furthermore, regression analysis used to control for gestation confirmed that UA PI had independent and significant variation between fetuses developing signs of intra-partum fetal compromise, and those that did not.

Results from this study suggest that, in a low risk pregnancy with an appropriately grown fetus, the UA PI in isolation has a limited role in risk stratification prior to labour. However in combination with the MCA PI in the C/U ratio its effectiveness is significantly improved.

Middle cerebral artery Doppler indices

Whilst the reduction in cerebral resistance in cases of fetal growth restriction is well documented[31], few studies have examined middle cerebral artery Doppler indices in appropriately grown infants at term.

Within the study population the MCA PI had a non-normal distribution secondary to a small degree of skewness and kurtosis. The kurtosis of the MCA PI distribution is likely a result of the target population being those with 'normal' pregnancies. With the exclusion of cases with recognised placental dysfunction, it was anticipated that a negative skew would be present within the population (towards higher MCA PI values), however this was not present. Morales-Rosello et al have reported that the degree of resistance in the MCA may be influenced by the proximity of term labour, with assessment of MCA resistance indices within 1-3 days of labour demonstrating a reduction in impedance indices[(354)].Within the term labour cohort of this study, 96% of cases underwent ultrasound assessment within three days of delivery, and 19.7% of all cases were in spontaneous labour. A reduction in impedance results in a lower MCA PI, thus the proximity to labour may be responsible for the positive skew observed in the MCA PI values.

Signification variation in MCA PI between the different mode of delivery groups was observed. Fetuses subsequently delivered by emergency caesarean delivery for presumed fetal compromise had the lowest MCA PI, whilst those delivered by SVD had the highest MCA PI. Multiple comparison testing confirmed that the MCA PI in both groups of babies delivered for presumed fetal compromise (caesarean and instrumental) were significantly different from the SVD group. Receiver-operator-characteristic curve analyses demonstrated that MCA PI was a significant predictor of subsequent caesarean delivery for presumed fetal compromise, with an AUC of 0.63, slightly better than that of the UA PI (AUC 0.61). These results suggest that some fetuses that subsequently develop signs of compromise during labour already have a relatively reduced cerebral resistance prior to the onset of active labour.

When divided into centile groups according to MCA PI value, fetuses with the lowest MCA PI ($<10^{th}$ centile) were at significantly increased risk of subsequently requiring delivery by emergency caesarean section for presumed fetal compromise, with a relative risk of 4.67 (95% CI 1.42-15.30) compared to those with an MCA PI $>90^{th}$ centile. Fetuses with the lowest MCA PI values were also significantly more likely to be diagnosed with fetal compromise at any time during labour and significantly less likely to be born by SVD.

Studies of middle cerebral artery Doppler indices in small for gestational age fetuses with normal umbilical artery Doppler indices have suggested that a low MCA PI indicative of increased cerebral perfusion can occur in the absence of evidence of increased placental resistance, and that such a finding may be correlated with increased incidence of caesarean delivery as well as the need for neonatal unit admission[213]. Data from the current study goes further, suggesting a relationship between MCA PI and the ability of the fetus to tolerate labour exists not only in fetuses that are small for gestational age, but also in appropriately grown fetuses in normal pregnancies.

Maternal demographics were compared between the different MCA PI centile groups. Only gestation varied significantly, with a lower mean gestation found in the group of fetuses with the highest MCA PI. Published reference ranges have identified that MCA PI peaks around 28 weeks gestation before following a gradual decline until term[185]. As was observed for the UA PI, the absolute difference in gestation was small (1.7 weeks), and so gestation was not considered to be a significant confounding variable. This is supported by the weak correlation between MCA PI and gestation in data from this study (see Figure 15), and also by regression analysis which confirmed that even when gestational age is controlled for, the MCA PI continues to have significant variation between fetuses subsequently developing signs of fetal compromise in labour and those that did not.

When intra-partum outcomes were examined, MCA PI was observed to vary significantly between the intra-partum FHR classification groups, with multiple comparison testing demonstrating that the MCA PI in fetuses with normal intra-partum monitoring is significantly different to that of both the 'suspicious' and 'pathological' groups. In contrast to UA PI, MCA PI was also observed to have significant variation between fetuses with meconium stained liquor and those without. Leung et al demonstrated in 2006 that low MCA PI, measured prior to external cephalic version, could be used to predict caesarean section for non-reassuring intra-partum FHR patterns[217]. Middle cerebral artery PI has also been found to be a significant independent predictor of the presence of meconium stained liquor in uncomplicated post-dates pregnancies[218]. Our results suggest that a fetus with a MCA PI <10th centile has close to a 30% chance of being diagnosed with a pathological CTG during labour, five times higher than that of a fetus with an MCA PI >90th centile (RR 5.0 95% CI 1.54 – 16.29).

Date from this study supports the suggestion that MCA PI may have potential use in the risk stratification of normal pregnancies. Used in isolation this marker may be more predictive

of fetal compromise than the UA PI, but still has a low positive predictive value for caesarean delivery for presumed fetal compromise (26%).

Measurement of the MCA Doppler indices at term is facilitated by the position of the fetal head, which frequently engages in a transverse position, making insonation of the MCA at a 0-30 degree angle feasible. The inter-observer and intra-observer variability recorded for the MCA PI were both acceptable and similar to other published series[355].

Cerebro-umbilical ratio

The clinical utility of the C/U ratio was first proposed in 1987, when it was observed that in pregnancies complicated by hypertension or fetal growth restriction the ratio of the MCA PI to UA PI was frequently <1[356]. However, consistent with other studies of fetal haemodynamics, much of the work related to the C/U ratio has taken place in cohorts of growth restricted fetuses.

Within this study population, the C/U ratio had a non-normal distribution. The reasons for this distribution are likely to be similar to those detailed for the UA PI and MCA PI in the previous sections.

Significant variation in the C/U ratio was observed between the different mode of delivery groups. The absolute difference in C/U ratio between the groups (0.27) was greater than that of both the UA PI and the MCA PI. Despite this, overlap in C/U ratio values was still present between the various modes of delivery groups. Multiple comparison testing confirmed that C/U ratios were significantly lower in fetuses delivered by caesarean section for presumed fetal compromise, than in all other mode of delivery groups, except the instrumental for fetal compromise group. These results demonstrate that fetuses that subsequently require delivery by emergency caesarean section for presumed fetal compromise have relatively increased placental resistance and reduced cerebral resistance, features suggestive of relatively reduced placental function and increased cerebral perfusion respectively. Cerebral redistribution is a physiological phenomenon seen in term fetuses, with longitudinal reference ranges confirming that following a peak at 30 weeks, the C/U ratio declines with advancing gestation[357].

Fetuses with the lowest C/U ratios prior to established labour were 21 times more likely to require caesarean section for presumed fetal compromise than those with the highest C/U ratios. From the current data, a C/U ratio >90th centile appears to be very protective, given that only one of 58 cases in this group required caesarean delivery for presumed fetal compromise. This particular case is also notable as a caesarean was performed due to a catastrophic fetal bradycardia, prior to established uterine contractions, suggestive of an abrupt and significant interruption of placental function. The C/U ratio may be a better predictor of caesarean delivery for presumed fetal compromise than either UA PI or MCA PI alone. Although the difference in the ROC curve AUC for the UA PI, MCA PI and C/U ratio was not statistically significant in this study cohort, logistic regression analysis did confirm that the C/U ratio was predictive of caesarean delivery for presumed fetal compromise even following adjustment for the influence of MCA PI or UA PI, suggesting it is a better predictor than either UA PI or MCA PI alone. Furthermore, ROC curve AUC comparison compares the performance of the predictive variables throughout their range of numerical values. Given that the potential predictive value of these variables lies at the upper and lower end of the ranges (<10th centile and >90th centile), comparing their predictive value across the entire range of numerical values may not be appropriate. A C/U ratio <1.24 (< 10th centile) was associated with a positive predictive value for caesarean section for presumed fetal compromise of 36%, whilst a C/U ratio >2.33 (>90th centile) was associated with a 98.3% negative predictive value. Fetuses with a C/U ratio >90th centile had an 85% vaginal delivery rate.

The C/U ratio is reported to be an accurate method of identifying cerebral redistribution with animal models confirming that the C/U ratio is a better predictor of fetal hypoxia than either the umbilical artery or middle cerebral artery alone[358]. Evaluation of the C/U ratio in growth restricted fetuses demonstrates that low values are also associated with reduced cord arterial pH and Apgar scores at delivery, as well as increased caesarean section rates[359]. The results from this study suggest that a correlation between the incidence of caesarean section for presumed fetal compromise and low C/U ratio values also exists amongst appropriately grown fetuses.

Gestation was the only maternal demographic characteristic to have significant variation between the different C/U ratio centile groups. Data from this study suggests a weak correlation between gestational age and C/U ratio (Figure 17), with a gradual decline

observed with advancing gestation. Longitudinal studies have also demonstrated that the C/U ratio peaks around 34 weeks gestation before following a gradual decline until term[241]. The finding of significantly higher mean gestational age in the group of infants with the lowest C/U ratios is thus consistent with previous published data, but unlikely to represent a confounding variable as the absolute difference in gestation between the three groups was small (1.4 weeks). Furthermore, regression analysis used to control for the variation in gestation confirmed the C/U ratio was a significant independent predictor of caesarean section for presumed fetal compromise.

The C/U ratio was also found to have significant variation between infants subsequently diagnosed with normal, suspicious, or pathological FHR patterns, with fetuses with pathological FHR patterns having the lowest mean C/U ratio. Cases with a C/U ratio <10th centile were four times more likely to have a pathological fetal heart rate pattern during labour than those with a C/U ratio >90th centile. Murata et al reported that the C/U ratio, measured in small for gestational age fetuses, could be used to predict a non-reassuring fetal heart rate patterns[360]. Results from the early labour cohort in this study suggest that the C/U ratio is also predictive of abnormal fetal heart rate patterns in an appropriately grown cohort.

The results from this study, suggest the C/U ratio may be a better predictor of subsequent intra-partum fetal compromise and the need for emergency delivery than either UA PI or MCA PI alone. Despite this, the positive predictive value of a low C/U ratio for emergency caesarean delivery for presumed fetal compromise was still relatively low (36%). In contrast the negative predictive value offered by a high C/U ratio is very good. The C/U ratio therefore does have potential to be used for the risk stratification of normal pregnancies prior to labour.

Umbilical venous flow

Adequate umbilical venous blood flow delivering oxygen and nutrients is essential to support the fetus within the uterine environment. The rate of umbilical venous flow may be considered a direct measure of the delivery of nutrients to the fetus by the placenta. Despite being first measured in the 1980s[361], the clinical utility of Umbilical venous flow measurement remains unknown. Studies of umbilical venous flow have demonstrated reduced flow rates in growth restricted fetuses[222, 362], and in cases of growth restriction, umbilical venous flow is reduced prior to changes in umbilical artery resistance[223]. Furthermore, abnormalities in umbilical venous flow have been associated with an increased incidence of operative delivery for fetal compromise[230].

Both UV flow and corrected UV flow had non-normal distributions within the study population. Both distributions had a small positive skew, and significant kurtosis. As reduced umbilical venous flow rates are associated with growth restriction[220, 222], the exclusion of such cases is likely to be responsible for the kurtosis of the study population and its non-normal distributions.

Results from the early labour cohort demonstrate that both UV flow and UV flow corrected for birthweight had significant variation between the different mode of delivery groups. The lowest UV flow rate and corrected UV flow rate were found in fetuses which subsequently required emergency delivery for presumed fetal compromise, whilst the highest rates were found in fetuses subsequently delivered by instrumental delivery for a prolonged 2nd stage. The variation in flow rate was secondary to variations in both umbilical venous flow velocity and umbilical vein diameter, as both these parameters also had significant independent variation between the mode of delivery groups. There was considerable overlap in UV flow and corrected UV flow values between the groups, but multiple comparison testing confirmed that in the case of UV flow, cases delivered by emergency caesarean delivery for presumed fetal compromise were significantly different to those born by SVD. For corrected UV flow, a significant difference was only confirmed between the caesarean for fetal compromise group and the instrumental for prolonged 2nd stage group. The absolute variation in both UV flow and corrected UV flow between the mode of delivery groups was small (28.9ml/min and 6.8ml/min/kg respectively). However, despite this, both cases with the lowest UV flow and those with the lowest corrected UV, were at significantly increased risk of a diagnosis of fetal compromise during labour. The variation in UV flow between the mode of delivery groups was greater than that of corrected UV flow, this finding, in

conjunction with the significant correlation observed between UV flow and birthweight, suggest that the variation in UV flow may be confounded to an extent by variations in birthweight.

Very little information is available regarding umbilical venous flow rates in appropriately grown fetuses, but an association between reduced UV flow rates and poor neonatal outcomes has been observed[363]. The median value for corrected umbilical venous flow rate in our study was 60.2ml/min/kg. Various studies have examined corrected umbilical venous flow rate at differing gestations[222, 364], but few have examined umbilical venous flow rates in appropriately grown fetuses at term. Acharya et al reported a 50th centile value for corrected umbilical venous flow rate at 40 weeks gestation of 65.86ml/min/kg[234], with measurements of vessel diameter and umbilical flow velocity measured at the intra-abdominal portion of the vessel. In our study we chose to measure both the umbilical vein diameter and flow velocity at a free loop of cord. Whilst umbilical vein diameter has been observed to decrease from the fetus to the placenta, acquiring accurate ultrasound images of the umbilical vein at both a 0 degree and 90 degree angle to determine diameter and velocity respectively are most easily achieved at a free loop of cord[328]. The methodological differences between this study and that of Acharya et al, may explain the slightly lower umbilical venous flow rate reported in the current study.

Results from the early labour cohort demonstrate that fetuses with the lowest UV flow and corrected UV flow rates are at a significantly increased risk of being diagnosed with fetal compromise during labour. Umbilical venous flow rate, along with the fetal C/U ratio, may therefore have potential value in risk stratification of normal pregnancies prior to labour.

Uterine artery PI

Adequate uterine artery flow velocity waveforms could only be recorded in 76.2% (460/604) of cases. Uterine artery measurements were performed using a trans-abdominal approach, as this was considered less invasive to the patient than a trans-vaginal approach. Several authors have observed that imaging of the uterine arteries is best achieved via the trans-vaginal approach[331, 365]. It is therefore possible that trans-vaginal ultrasound may have yielded adequate flow velocity waveforms in a greater proportion of patients. Consideration of an alternative to the trans-abdominal approach would be important for any further studies that involved imaging the uterine artery at term.

Reference ranges for uterine artery PI have been published. Gomez et al reported a 50th centile value for the uterine artery PI of 0.65 at 40 weeks, with 5th and 95th centile values of 0.47 and 0.90 respectively[331]. In the early labour cohort, uterine artery PI had a 50th centile value of 0.70 with 5th and 95th centile values of 0.45 and 1.16 respectively, similar to those previously reported.

No significant variation in uterine artery values was observed between the different mode of delivery groups. Whilst abnormal uterine artery Doppler is associated with the development fetal growth restriction and pre-eclampsia[366], other studies have also reported the absence of an association between uterine artery PI and the development of fetal compromise in labour[367]. An increased likelihood of intra-partum fetal compromise has been reported in small for gestational age fetuses, with concurrent raised uterine artery PI[368, 369]. However, in these studies small for gestational age was an inclusion criterion, whilst such babies were specifically excluded from the population of the current study. Data from the early labour cohort suggests that, in appropriately grown babies, uterine artery PI does not correlate with the ability of the fetus to tolerate labour. Interestingly, in pre-eclampsia, another condition accepted to result from placental dysfunction, the late onset variant has not been associated with abnormal placentation or raised uterine artery PI[370]. It is therefore possible that deterioration in placental function in late gestation, resulting in the development of fetal compromise during labour, could also occur without any significant alteration in uterine artery resistance.

Amniotic fluid volume

Amniotic fluid volume was investigated using both the amniotic fluid index and the deepest vertical pool as measures. Reduced amniotic fluid volumes have a strong association with fetal growth restriction secondary to placental insufficiency[256], but amniotic fluid volume has been suggested to be only a poor predictor of subsequent neonatal outcome[264].

Both AFI and DVP had a non-normal distribution within the study population with a small positive skew and significant kurtosis. As expected within a population of normal pregnancies, the incidence of markedly low amniotic fluid volumes was small.

Whilst no significant association between AFI or DVP was observed between the mode of delivery groups, the lowest AFI and DVP were found in the group delivered by emergency caesarean for presumed fetal compromise, and the second lowest in those delivered by instrumental delivery for presumed fetal compromise. These trends bordered statistical significance ($p = 0.06$), and may have reached significance with a larger study population. However, the absolute difference in both measures between the mode of delivery groups was small (1.2 for AFI and 0.7 for DVP), meaning that even if significant variation was observed, its clinical value may be limited. Significant variation in AFI and DVP was observed between the intra-partum FHR classification groups, with the highest AFI and DVP found in cases with 'normal' intra-partum monitoring. Multiple comparison testing confirmed that the AFI in cases with 'normal' monitoring was significantly different to that of both the 'suspicious' and 'pathological' groups, but found no significant differences in DVP between the groups. Oligohydramnios is associated with the occurrence of variable decelerations on fetal heart rate monitoring, thought to occur secondary to compression of the umbilical cord[371]. Amnio-infusion has been suggested as a method with which to eliminate such fetal heart rate abnormalities, and has been reported to result in reduced use of caesarean delivery as a result[372]. The absence of significant variation in DVP between the intra-partum monitoring groups despite a significant variation in AFI is interesting, considering both AFI and DVP are reported to have an equally poor correlation with abnormal amniotic fluid volumes when measured using the dye dilution technique[373]. Amniotic fluid index has been suggested to be less preferable than DVP due to a propensity to over diagnose oligohydramnios, resulting in greater intervention rates without concurrent improvements in perinatal outcomes[374]. In contrast, data from the current study would appear to suggest that whilst neither AFI nor DVP is a good predictor of subsequent intra-partum outcomes,

AFI performs marginally better. However, overall these results support the conclusions of previous publications that amniotic fluid volume is a poor predictor of intra-partum outcomes.

Neonatal outcomes

This study was not powered to detect differences in neonatal outcomes. However several interesting findings were noted. The highest incidence of low Apgar score, cord arterial pH <7.20, cord arterial base excess <-8.0mmol/L, and the highest composite neonatal outcome score, were all found in the group of infants delivered by instrumental delivery for presumed fetal compromise. In contrast, the group of infants delivered by emergency caesarean section for presumed fetal compromise had an incidence of cord arterial pH <7.20 and base excess <-8.0, lower than that of the SVD group. These infants also had the second lowest composite neonatal outcome score, being higher than only the emergency caesarean 'other' group. Infants born by SVD had the second highest composite neonatal outcome score of all mode of delivery groups. These findings are interesting as whilst significant variation in the neonatal outcome variables was observed, the differences between the mode of delivery groups were not as anticipated, with infants delivered by caesarean section for presumed fetal compromise having better neonatal outcomes than other delivery modalities.

The only other significant association between the ultrasound parameters and the neonatal outcomes variables was a higher incidence of neonatal unit admission amongst cases with an MCA PI >90th centile. This finding is interesting as these cases were significantly less likely to be diagnosed with intra-partum compromise during labour. Further analysis of the three cases in this group that required neonatal unit admission found that none were diagnosed with fetal compromise during labour, and only one had an umbilical artery pH <7.20 at delivery. In all three cases the reason for admission to the neonatal unit was sepsis, rather than concerns regarding hypoxia.

Whilst the absence of an association between the ultrasound parameters and neonatal outcome variables in this study, may be considered evidence of an absence of association with true (as opposed to presumed) intra-partum fetal compromise, it is considered likely that these commonly used measures of adverse neonatal outcomes are in themselves, poor identifiers of true intra-partum compromise. These parameters are representative of the neonatal condition at delivery, rather than at the time of the decision for delivery. There is potential for them to be influenced by events occurring between these time points. The cessation of syntocinon prior to emergency caesarean section may result in a better than expected neonatal condition at delivery, whilst a difficult instrumental delivery may result in a worse than expected neonatal condition.

The influence of fetal weight on intra-partum outcomes

Multiple investigations have demonstrated that fetuses with growth restriction are at increased risk of developing signs of compromise during labour and requiring emergency delivery. Other studies have also suggested that fetuses that fail to meet their growth potential, although >10th centile in birthweight, are at increased risk of CTG abnormalities in labour and operative delivery[375]. Results from the early labour cohort demonstrate that even amongst a cohort of apparently appropriately grown fetuses, both birthweight and birthweight centile have significant variation between the different mode of delivery groups. Multiple comparison testing confirmed that cases born by instrumental delivery for a prolonged 2nd stage, and emergency caesarean 'other' were significantly larger than those in other mode of delivery groups. The study population did contain 41 cases with a birthweight <10th centile, and whilst no significant difference in the incidence of fetal compromise or FHR abnormalities was observed between these cases and those with a birthweight ≥10th centile, the SGA group did have the highest incidence of caesarean for presumed fetal compromise, and the highest incidence of pathological FHR patterns. This study was not powered to examine this outcome, and it is possible that an appropriately powered study would demonstrate significant differences between SGA infants and their AGA counterparts. The ultrasound derived estimated fetal weights in this study had a good correlation with actual birthweight (within 10% in 75.5% of cases and within 15% in 91.7%), and were consistent with correlations of estimated fetal weight and birthweight reported in other studies [376, 377].

Potential limitations of this study include the method of diagnosis of intra-partum compromise. It is acknowledged that in cases of intra-partum fetal compromise, the diagnosis is presumptive, based on clinical interpretation of the fetal heart rate patterns supplemented by the clinical scenario (meconium liquor, maternal pyrexia etc.) Due to the identified problems of using neonatal outcome variables as markers of compromise, and the absence of a gold standard test for intra-partum fetal compromise, it was considered reasonable to use the clinical diagnosis of fetal compromise as a surrogate for true fetal compromise. Potential limitations of Doppler ultrasound assessment were addressed in this study. All scans were performed by a single operator, removing any inter-observer variability. All Doppler parameters were calculated using an automated waveform tracing of at least three consecutive waveforms. For each case, Doppler readings were taken in triplicate, and the mean value used for data analysis. All umbilical artery Doppler

parameters in this study were sampled from a free loop of cord, with an angle of insonation between 0-30 degrees, and in the absence of fetal breathing movements to ensure accurate waveforms were recorded. Previous studies have suggested the UA PI recordings vary along the length of the cord, with the highest values being recorded in the intra-abdominal portion of the cord, and values falling progressively towards the placental insertion[327, 378]. It has also been observed that there is a greater discrepancy in the PI values between the two umbilical arteries at the intra-abdominal portion[378]. We chose the free loop as the sampling site in our study as it is the most commonly sampled site in clinical practice and the most commonly used site for the creation of reference ranges of UA PI[185, 379]. The free loop is also the simplest sampling site technically, particularly in a full term pregnancy. Middle cerebral artery and uterine artery waveforms were acquired in accordance with current guidelines[169].

Summary and key findings

Results from the early labour phase of this study have demonstrated that several ultrasound markers of fetal wellbeing, measured prior to active labour, can identify fetuses at high and low risk of a subsequent diagnosis of intra-partum fetal compromise. Fetuses at increased risk of compromise in labour have a haemodynamic profile similar to that found in cases of growth restriction.

The C/U ratio appears to be more predictive of Caesarean delivery for presumed fetal compromise than either the UA PI or MCA PI used in isolation.

Chapter 4 – Ultrasound assessment at 35 - 37 weeks gestation

Following the observation of an association between ultrasound derived markers of fetal wellbeing measured in early labour, and clinical signs of intra-partum fetal compromise, we sought to determine if a similar relationship existed between these ultrasound parameters when measured earlier in pregnancy. An ultrasound assessment, identical to that performed during early labour in the previous chapter, was undertaken between 35 and 37 weeks, a gestation that coincided with a routine antenatal clinic appointment and was therefore not too inconvenient for women who participated in this study.

Aim

To ascertain the utility of ultrasound derived markers of fetal wellbeing, measured between 35 and 37 weeks gestation, and subsequent intra-partum and neonatal outcomes.

Methods

This prospective observational study was undertaken over a 12 month period between July 2012 and July 2013, at Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare Trust, London, UK. This was a proof of concept study, with a minimum target recruitment of 100 cases, similar to the previously conducted pilot study. Recruitment to the study was undertaken using advertisements placed in the antenatal clinic, day assessment unit, and ultrasound department at Queen Charlotte's Hospital. An ultrasound assessment for each participant was scheduled for between 35 and 37 weeks gestation. Informed written consent was obtained from all patients according to the protocol described in the previous chapter.

The procedure and technique for ultrasound assessment was identical to that of the early labour phase of the project. All ultrasound scans were performed by a single practitioner (Dr Tomas Prior) using a GE Voluson e portable ultrasound machine, and an AB2-7RS curvilinear trans-abdominal probe. After completion of the ultrasound assessment, patients were managed as per local protocols and guidelines. A formal ultrasound report was completed and filed in the participants' handheld maternity notes. If any fetal concerns were raised by the ultrasound assessment the participant was referred for further investigation/management as required. Following delivery, each case was followed up within 48 hours by review of case notes and electronic records.

The study outcomes and methods of data analysis were identical to those described in the previous chapter.

Results

Recruitment to this phase of the project ran from July 2012 until July 2013. One hundred and twenty five participants were recruited over this 12 month time period. All participants underwent an ultrasound assessment between 35 and 37 weeks gestation, and went on to deliver live infants. Eight percent (10/125) were delivered by elective caesarean. Of these, breech presentation accounted for 4.8% (6/125) and maternal request for 3.2% (4/125). Emergency caesarean sections were performed in 17.6% (22/125), of cases with an indication of presumed fetal compromise in 8% (10/125) and failure to progress in 8% (10/125). The remaining two emergency caesarean deliveries were performed for unstable lie in one case, and maternal sepsis in one case. Instrumental deliveries were performed in 36.0% (45/125) of cases, with an indication of presumed fetal compromise in 17.6% (22/125) and failure to progress in the 2nd stage in 18.4% (23/125) of cases. The remaining 38.4% (48/125) were delivered by SVD.

Cases delivered by elective caesarean section were removed from further data analysis yielding a study population of 115 cases.

Maternal demographics

Details of maternal demographics were documented from the Obstetric notes (Table 60).

	Overall
Number of Patients	115
% Nulliparous	86.0% (99/115)
Mean Maternal Age	32.3 (20 – 45)
Median BMI	23.0 (17 – 115)
Mean gestation (weeks)	36.3 (35.0 – 37.0)
Ethnicity (%)	
Caucasian	76.5% (88/115)
Asian	17.4% (20/115)
Afro-Caribbean	4.3% (5/115)
Other	1.7% (2/115)
Mode of onset of labour (%)	
Induction	24.3% (28/115)
Spontaneous	75.7% (87/115)

Table 62. Maternal demographics

The maternal demographics of the 36 week cohort were compared to those of the early labour cohort. The 36 week cohort had a significantly lower proportion of cases whose mode of onset of labour was induction ($p = <0.001$), and a significantly higher proportion of cases with spontaneous onset of labour ($p = <0.001$). No other significant differences were identified between the two study populations. The median interval between ultrasound assessment and delivery was 4.0 weeks (range 0.1 – 7.0).

Relationship between ultrasound parameters measured at 35-37 weeks gestation and subsequent labour outcomes

Umbilical artery PI

The umbilical artery PI had a normal distribution within the study population (Skewness = 0.29, Kurtosis = -0.38, D'agostino-Pearson p = 0.29). The mean UA PI was 0.83 (range 0.55 – 1.20), with a 10^{th} centile value of 0.64 and a 90^{th} centile value of 1.02.

Cases were sub-divided according to the subsequent mode of delivery and the UA PI compared between these groups (Table 61). No significant variation in UA PI was observed between the different mode of delivery groups. Bonferroni's multiple comparison test confirmed that no individual mode of delivery group's mean UA PI differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	ANOVA
Number of Patients	115	10	22	48	23	12	
UA PI	0.83 (0.55 – 1.20)	0.82 (0.64 – 1.02	0.80 (0.57 – 1.18)	0.85 (0.60 – 1.13)	0.83 (0.64 – 1.20)	0.81 (0.55 – 1.04)	0.56

Table 63. UA PI according to mode of delivery group

Cases were grouped according to UA PI values of <10^{th} centile, 10^{th} – 90^{th} centile and >90^{th} centile and mode of delivery outcomes compared between the groups (Table 62). No significant variation in mode of delivery outcomes was identified between the UA PI centile groups.

Delivery category	Overall	UA PI <10^{th} Centile	UA PI 10^{th}-90^{th} Centile	UA PI >90^{th} Centile	X^2 p=	Relative risk <10^{th} and >90th
Caesarean section Fetal compromise	8.7% (10/115)	0.0% (0/6)	10.2% (10/98)	0.0% (0/11)	0.42	n/a
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	66.7% (4/6)	26.5% (26/98)	18.2% (2/11)	0.16	3.67 95% CI 0.93 – 14.50
SVD	41.7% (48/115)	33.3% (2/6)	39.8% (39/98)	63.6% (7/11)	0.48	0.52 95% CI 0.16 – 1.77
Vaginal delivery of any kind	80.9% (93/115)	83.3% (5/6)	79.6% (78/98)	91.0% (10/11)	0.92	0.92 95% CI 0.61 – 1.37
Caesarean section other	10.4% (12/115)	16.7% (1/6)	10.2% (10/98)	9.1% (1/11)	0.88	1.83 95% CI 0.14 – 24.37

Table 64. Delivery outcomes according to UA PI centile group

Middle cerebral artery PI

The MCA PI had a non-normal distribution within the study population (Skewness = -0.10, Kurtosis = -0.80, D'agostino-Pearson p = 0.02). The median MCA PI was 1.67 (range 1.10 – 2.26) with a 10^{th} centile value of 1.27 and a 90^{th} centile value of 1.97. Cases were subdivided according to subsequent mode of delivery, and the MCA PI compared between each group (Table 63). No significant variation was observed between the different mode of delivery groups. Dunn's multiple comparison test confirmed that no individual mode of delivery group's MCA PI differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal-Wallis
Number of Patients	115	10	22	48	23	12	
MCA PI	1.67 (1.10 – 2.26)	1.66 (1.26 – 1.91)	1.72 (1.20 – 2.26)	1.66 (1.10 – 2.04)	1.65 (1.22 – 2.06)	1.74 (1.27 – 1.94)	0.98

Table 65. MCA PI according to mode of delivery group

Cases were grouped according to MCA PI values of <10^{th} centile, 10^{th} – 90^{th} centile and >90^{th} centile and mode of delivery outcomes compared between the groups (Table 64). No significant variation in mode of delivery outcomes was identified between the MCA PI centile groups.

Delivery category	Overall	MCA PI <10^{th} Centile	MCA PI 10^{th}-90^{th} Centile	MCA PI >90^{th} Centile	X^2 p=	Relative risk <10^{th} and >90th
Caesarean section Fetal compromise	8.7% (10/115)	10.0% (1/10)	9.6% (9/94)	0.0% (0/11)	0.59	n/a
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	40.0% (4/10)	27.7% (26/94)	18.2% (2/11)	0.64	2.2 95% CI 0.51 – 9.53
SVD	41.7% (48/115)	40.0% (4/10)	40.4% (38/94)	54.5% (6/11)	0.79	0.73 95% CI 0.29 – 1.86
Vaginal delivery of any kind	80.9% (93/115)	90.0% (9/10)	77.7% (73/94)	100% (11/11)	0.70	0.9 95% CI 0.73 – 1.11
Caesarean section other	10.4% (12/115)	0.0% (0/10)	12.8% (12/94)	0.0% (0/11)	0.26	n/a

Table 66. Delivery outcomes according to MCA PI centile group

Cerebro-umbilical ratio

The cerebro-umbilical ratio had a normal distribution within the study population (Skewness = 0.21, Kurtosis = 0.02, D'agostino-Pearson p = 0.62). The mean C/U ratio was 2.02 (range 1.17 – 3.21) with a 10^{th} centile value of 1.53 and a 90^{th} centile value of 2.53.

Cases were subdivided according to subsequent mode of delivery, and the C/U ratio compared between each group (Table 65). No significant variation was observed between the different mode of delivery groups. Bonferroni's multiple comparison test confirmed that no individual mode of delivery group's C/U ratio differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	ANOVA
Number of Patients	115	10	22	48	23	12	
C/U ratio	2.02 (1.17 – 3.21)	2.01 (1.34 – 2.64)	2.13 (1.64 – 2.70)	1.97 (1.17 – 3.21)	2.03 (1.49 – 2.55)	2.04 (1.59 – 2.53)	0.47

Table 67. C/U ratio according to mode of delivery group

Cases were grouped according to C/U ratio values of $<10^{th}$ centile, 10^{th} – 90^{th} centile and $>90^{th}$ centile and mode of delivery outcomes compared between the groups (Table 66). No significant variation in mode of delivery outcomes was identified between the C/U ratio centile groups.

Delivery category	Overall	C/U ratio $<10^{th}$ Centile	C/U ratio 10^{th}-90^{th} Centile	C/U ratio $>90^{th}$ Centile	X^2 p=	Relative risk $<10^{th}$ and >90th
Caesarean section Fetal compromise	8.7% (10/115)	18.2% (2/11)	7.4% (7/94)	10.0% (1/10)	0.52	1.82 95% CI 0.19 – 17.12
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	18.2% (2/11)	28.7% (27/94)	30.0% (3/10)	0.81	0.61 95% CI 0.13 – 2.92
SVD	41.7% (48/115)	63.6% (7/11)	37.2% (35/94)	60.0% (6/10)	0.28	1.06 95% CI 0.54 – 2.08
Vaginal delivery of any kind	80.9% (93/115)	81.8% (9/11)	79.8% (75/94)	90.0% (9/10)	0.94	0.91 95% CI 0.64 – 1.29
Caesarean section other	10.4% (12/115)	0.0% (0/11)	12.8% (12/94)	0.0% (0/10)	0.26	n/a

Table 68. Delivery outcomes according to C/U ratio centile group

Umbilical venous flow

Umbilical venous flow rate had a non-normal distribution in the study population (Skewness = 0.53, Kurtosis = 0.57, D'agostino-Pearson p = 0.03). The median UV flow rate was 231.7ml/min (range 92.7 – 412.1), with a 10^{th} centile value of 161.4ml/min and a 90^{th} centile value of 307.0. Cases were subdivided according to subsequent mode of delivery, and the UV flow rate compared between each group (Table 67). No significant variation was observed between the different mode of delivery groups. Dunn's multiple comparison test confirmed that no individual mode of delivery group's UV flow rate differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal-Wallis
Number of Patients	115	10	22	48	23	12	
UV flow (ml/min)	231.7 (92.7 – 412.1)	249.7 (125.7 – 295.7)	216.1 (146.0 – 384.6)	227.1 (92.7 – 399.8)	238.6 (173.6 – 412.1)	236.3 (142.9 – 335.6)	0.91

Table 69. UV flow rate according to mode of delivery group

Cases were grouped according to UV flow rate values of <10^{th} centile, 10^{th} – 90^{th} centile and >90^{th} centile and mode of delivery outcomes compared between the groups (Table 68). No significant variation in mode of delivery outcomes was identified between the UV flow rate centile groups.

Delivery category	Overall	UV flow rate <10^{th} Centile	UV flow rate 10^{th}-90^{th} Centile	UV flow rate >90^{th} Centile	X^2 p=	Relative risk <10^{th} and >90th
Caesarean section Fetal compromise	8.7% (10/115)	18.2% (2/11)	8.6% (8/93)	0.0% (0/11)	0.35	n/a
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	36.4% (4/11)	26.9% (25/93)	27.3% (3/11)	0.85	1.33 95% CI 0.39 – 4.62
SVD	41.7% (48/115)	54.5% (6/11)	40.9% (38/93)	36.4% (4/11)	0.77	1.50 95% CI 0.58 – 3.88
Vaginal delivery of any kind	80.9% (93/115)	72.7% (8/11)	80.6% (75/93)	90.9% (10/11)	0.89	0.80 95% CI 0.53 – 1.20
Caesarean section other	10.4% (12/115)	9.1% (1/11)	10.8% (10/93)	9.1% (1/11)	0.98	1.00 95% CI 0.01 – 14.05

Table 70. Delivery outcomes according to UV flow rate centile group

Corrected UV flow had a non-normal distribution in the study population (Skewness = 0.54, Kurtosis = 0.37, D'agostino-Pearson = 0.04). The median corrected UV flow rate was 65.0ml/min/kg (range 36.9 – 110.5) with a 10th centile value of 48.8ml/min/kg and 90th centile value of 93.5ml/min/kg.

Cases were subdivided according to subsequent mode of delivery, and the corrected UV flow rate compared between each group (Table 69). No significant variation was observed between the different mode of delivery groups. Dunn's multiple comparison test confirmed that no individual mode of delivery group's corrected UV flow rate differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal-Wallis
Number of Patients	115	10	22	48	23	12	
Corrected UV flow (ml/min/kg)	65.0 (36.9 – 110.5)	61.1 (42.3 – 85.1)	62.6 (45.9 – 110.5)	65.4 (36.9 – 107.2)	65.9 (49.0 – 106.8)	65.2 (43.9 – 96.4)	0.80

Table 71. Corrected UV flow rate according to mode of delivery group

Cases were grouped according to corrected UV flow rate values of <10th centile, 10th – 90th centile and >90th centile and mode of delivery outcomes compared between the groups (Table 70). No significant variation in mode of delivery outcomes was identified between the corrected UV flow rate centile groups.

Delivery category	Overall	Corrected UV flow rate <10th Centile	Corrected UV flow rate 10th-90th Centile	Corrected UV flow rate >90th Centile	X^2 p=	Relative risk <10th and >90th
Caesarean section Fetal compromise	8.7% (10/115)	18.2% (2/11)	8.6% (8/93)	0.0% (0/11)	0.35	n/a
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	27.3% (3/11)	29.0% (27/93)	18.2% (2/11)	0.81	1.50 95% CI 0.31 – 7.30
SVD	41.7% (48/115)	54.5% (6/11)	40.9% (38/93)	36.4% (4/11)	0.77	1.50 95% CI 0.58 – 3.88
Vaginal delivery of any kind	80.9% (93/115)	63.6% (7/11)	82.8% (77/93)	81.8% (9/11)	0.80	0.77 95% CI 0.46 – 1.32
Caesarean section other	10.4% (12/115)	18.2% (2/11)	72.7% (8/11)	18.2% (2/11)	0.46	1.00 95% CI 0.17 – 5.89

Table 72. Delivery outcomes according to corrected UV flow rate centile group

Amniotic fluid volume

Amniotic fluid volume was measured using the amniotic fluid index. Amniotic fluid index had a normal distribution in the study population (Skewness = 0.34, Kurtosis = 0.41, D'agostino-Pearson p = 0.19). The mean AFI was 12.7 (range 6.0 -22.0) with a 10^{th} centile value of 9.4 and a 90^{th} centile value of 16.5.

Cases were subdivided according to subsequent mode of delivery, and the AFI compared between each group (Table 71). No significant variation was observed between the different mode of delivery groups. Bonferroni's multiple comparison test confirmed that no individual mode of delivery group's AFI differed significantly from any other group.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	ANOVA
Number of Patients	115	10	22	48	23	12	
AFI	12.7 (6.0 – 22.0)	11.2 (7.9 – 15.5)	13.2 (9.7 – 19.5)	12.8 (6.0 – 18.0)	13.0 (6.8 20.2)	12.4 (9.3 – 22.0)	0.43

Table 73. AFI according to mode of delivery group.

Cases were grouped according to AFI values of $<10^{th}$ centile, 10^{th} – 90^{th} centile and $>90^{th}$ centile and mode of delivery outcomes compared between the groups (Table 72). No significant variation in mode of delivery outcomes was identified between the AFI centile groups.

Delivery category	Overall	AFI $<10^{th}$ Centile	AFI 10^{th}-90^{th} Centile	AFI $>90^{th}$ Centile	X^2 p=	Relative risk $<10^{th}$ and >90th
Caesarean section Fetal compromise	8.7% (10/115)	(3/11)	(7/93)	(0/11)	0.07	n/a
Fetal compromise diagnosed at any time during labour	27.8% (32/115)	(3/11)	(28/93)	(1/11)	0.46	3.00 95% CI 0.37 – 24.58
SVD	41.7% (48/115)	(4/11)	(39/93)	(5/11)	0.94	0.80 95% CI 0.29 – 2.21
Vaginal delivery of any kind	80.9% (93/115)	(7/11)	(76/93)	(10/11)	0.76	0.70 95% CI 0.43 – 1.14
Caesarean section other	10.4% (12/115)	(1/11)	(10/93)	(1/11)	0.98	1.00 95% CI 0.07 – 14.05

Table 74. Delivery outcomes according to AFI centile group

Relationship between ultrasound parameters measured at 36 weeks gestation and intra-partum outcomes

The incidence of intra-partum outcomes including the diagnosis of suspicious or pathological fetal heart rate patterns, and the incidence of meconium stained liquor were also evaluated for the 35 - 37 week cohort.

Intra-partum monitoring

Cases were sub-divided according to their intra-partum FHR classification (Table 73). Intra-partum FHR patterns were classified as normal in 47.0% (54/115) of cases, suspicious in 37.4% (43/115) of cases, and pathological in 15.7% (18/115) of cases. The incidence of normal intra-partum monitoring was significantly different to that of the early labour cohort ($p = 0.02$), whilst the incidence of suspicious and pathological intra-partum monitoring was not significantly different ($p = 0.20$ and $p = 0.33$ respectively). The ultrasound parameters were compared between the intra-partum monitoring groups but no significant variations were observed.

	FHR patterns – Normal	FHR patterns – suspicious	FHR patterns - pathological	Kruskal-Wallis/ANOVA p=
UA PI	0.86 (0.55 – 1.20)	0.79 (0.60 – 1.04)	0.83 (0.57 – 1.18)	0.07
MCA PI	1.65 (1.10 – 2.06)	1.69 (1.20 – 2.04)	1.79 (1.20 – 2.26)	0.39
C/U ratio	1.96 (1.17 – 2.74)	2.08 (1.34 – 3.21)	2.10 (1.46 – 2.53)	0.20
UV flow (ml/min)	232.7 (143.1 – 412.1)	239.8 (125.7 – 399.8)	213.7 (92.7 – 295.7)	0.16
Corrected UV flow (ml/min/kg)	65.3 (39.4 – 106.8)	65.0 (42.3 – 110.5)	62.6 (39.9 – 93.3)	0.50
AFI	13.0 (6.0 – 22.0)	12.5 (7.9 – 19.5)	12.6 (9.3 – 16.6)	0.68

Table 75. Ultrasound parameters according to intra-partum FHR classification

Meconium stained liquor

Meconium stained liquor was documented in 14.8% (17/115) of cases. This incidence was not significantly different from that of the early labour cohort (p = 0.51). The ultrasound parameters were compared between cases with and without meconium stained liquor, but no significant variations were observed (Table 74).

	Clear liquor	Meconium stained liquor	p=
UA PI	0.84 (0.55 – 1.20)	1.04 (0.57 – 0.88)	0.37
MCA PI	1.66 (1.10 – 2.26)	1.72 (1.20 - 1.99)	0.66
C/U ratio	2.01 (1.17 – 2.74)	2.12 (1.63 – 3.21)	0.25
UV flow (ml/min)	236.0 (92.7 – 412.1)	212.5 (129.5 – 357.3)	0.25
Corrected UV flow (ml/min/kg)	65.7 (36.9 – 110.5)	59.8 (49.0 – 99.8)	0.11
AFI	12.8 (6.0 – 22.0)	12.1 (8.2 – 16.6)	0.35

Table 76. Ultrasound parameters according to liquor status

Relationship between ultrasound parameters measured at 36 weeks gestation and neonatal outcomes

Neonatal outcome variables were compared between the different mode of delivery groups (Table 75). Only the incidence of an Apgar score less than seven at five minutes had significant variation between the mode of delivery groups.

	Overall	Emergency caesarean Fetal compromise	Instrumental Fetal Compromise	SVD	Instrumental Prolonged 2nd stage	Emergency caesarean other	ANOVA/ X^2 p=
Mean Birthweight (g)	3426 (2440 – 4566)	3546 (2482 – 4320)	3353 (2700 – 4092)	3367 (2440 – 4080)	3483 (2700 – 4100)	3590 (3114 – 4566)	0.29
Median Birthweight centile	45.0 (2 – 100)	35.0 (4 – 91)	66.0 (2 – 97)	40.5 (2 – 92)	56.0 (5 – 91)	49.5 (20 – 100)	0.33
Incidence Apgar <7 at 1 min	7.8% (9/115)	20.0% (2/10)	18.2% (4/22)	0.0% (0/48)	8.7% (2/23)	8.3% (1/12)	0.07
Incidence Apgar <7 at 5 min	0.9% (1/115)	10.0% (1/10)	0.0% (0/22)	0.0% (0/48)	0.0% (0/23)	0.0% (0/12)	0.04
Incidence Cord arterial pH < 7.20	22.6% (26/115)	60.0% (6/10)	22.7% (5/22)	18.8% (9/48)	21.7% (5/23)	8.3% (1/12)	0.11
Incidence Base Excess < -8	16.5% (19/115)	20.0% (2/10)	22.7% (5/22)	14.6% (7/48)	13.0% (3/23)	16.7% (2/12)	0.93
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/10)	0.0% (0/22)	0.0% (0/48)	4.3% (1/23)	0.0% (0/12)	0.42
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/10)	0.0% (0/22)	0.0% (0/48)	0.0% (0/23)	0.0% (0/12)	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	1.20 (0 – 3)	0.38 (0 – 3)	0.68 (0 – 3)	0.48 (0 – 3)	0.42 (0 – 4)	0.06

N.b Composite Neonatal outcome scored as follows

5. **Apgar - >7 @ 1 min = 0, <7 @ 1 min =1, <7 @5 min = 2**
6. **Cord arterial pH - >7.20 = 0, <7.20 = 1, <7.10 = 2, < 7.00 = 3**
7. **Base excess - >-8 = 0, <-8 and >-12 = 1, <-12 = 2**
8. **NNU admission - No = 0, Yes = 1**

Table 77. Comparison of neonatal outcome variables between mode of delivery groups

The neonatal outcome variables were then compared between the centile groups for each ultrasound parameter.

Relationship between neonatal outcome variables and umbilical artery PI, MCA PI and the C/U ratio

None of the neonatal outcome variables had significant variation between the UA PI, MCA PI and C/U ratio centile groups (Tables 76, 77 and 78).

	Overall	UA PI <10th Centile	UA PI 10th-90th Centile	UA PI>90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	3327 (2720 – 3730)	3436 (2440 – 4566)	3397 (3160 – 3780)	0.79	n/a
Median Birthweight centile	45.0 (2 – 100)	39.2 (4 – 71)	48.5 (2 – 100)	43.6 (21 – 87)	0.69	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	16.7% (1/6)	8.2% (8/98)	0.0% (0/11)	0.48	n/a
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/6)	1.0% (1/98)	0.0% (0/11)	0.92	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	16.7% (1/6)	23.5% (23/98)	18.2% (2/11)	0.90	0.92 95% CI 0.10 – 8.15
Incidence Base Excess < -8	16.5% (19/115)	33.3% (2/6)	16.3% (16/98)	9.1% (1/11)	0.50	3.67 95% CI 0.41 – 32.59
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/6)	1.0% (1/98)	0.0% (0/11)	0.92	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/6)	0.0% (0/98)	0.0% (0/11)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.83 (0 – 3)	0.36 (0 – 4)	0.27 (0 – 1)	0.56	n/a

Table 78. Comparison of neonatal outcome variables between UA PI centile groups

	Overall	MCA PI <10th Centile	MCA PI 10th-90th Centile	MCA PI>90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	3159 (2510 – 3740)	3467 (2440 – 4566)	3323 (2640 – 4100)	0.05	n/a
Median Birthweight centile	45.0 (2 – 100)	33.0 (2 – 69)	47.0 (2 – 100)	39.0 (4 – 91)	0.09	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	10.0% (1/10)	8.5% (8/94)	0.0% (0/11)	0.61	n/a
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/10)	1.1% (1/94)	0.0% (0/11)	0.90	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	10.0% (1/10)	24.5% (23/94)	18.2% (2/11)	0.62	0.55 95% CI 0.06 – 5.18
Incidence Base Excess < -8	16.5% (19/115)	30.0% (3/10)	16.0% (15/94)	9.1% (1/11)	0.48	3.30 95% CI 0.41 – 26.81
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/10)	1.1% (1/94)	0.0% (0/11)	0.90	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/10)	0.0% (0/94)	0.0% (0/11)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.50 (0 – 2)	0.56 (0 – 4)	0.27 (0 – 1)	0.76	n/a

Table 79. Comparison of neonatal outcome variables between MCA PI centile groups

	Overall	C/U ratio <10th Centile	C/U ratio 10th-90th Centile	C/U ratio >90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	3290 (2510 – 3950)	4566 (2440 – 4566)	3456 (2580 – 4060)	0.51	n/a
Median Birthweight centile	45.0 (2 – 100)	36.0 (2 – 84)	46.5 (2 – 100)	59.5 (2 – 90)	0.71	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	0.0% (0/11)	8.5% (8/94)	10.0% (1/10)	0.61	n/a
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/11)	1.1% (1/94)	0.0% (0/10)	0.90	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	18.2% (2/11)	23.4% (22/94)	20.0% (2/10)	0.93	0.91 95% CI 0.16 – 5.30
Incidence Base Excess < -8	16.5% (19/115)	36.4% (4/11)	14.9% (14/94)	10.0% (1/10)	0.22	3.64 95% CI 0.48 – 27.33
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/11)	1.1% (1/94)	0.0% (0/10)	0.90	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/11)	0.0% (0/94)	0.0% (0/10)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.55 (0 – 2)	0.53 (0 – 4)	0.50 (0 – 3)	0.95	n/a

Table 80. Comparison of neonatal outcome variables between C/U ratio centile groups

Relationship between neonatal outcome variables and umbilical venous flow rate

Both birthweight and birthweight centile had significant variation between the different UV flow rate centile groups (Table 79). Infants with the highest UV flow rates had the largest birthweight and greatest birthweight centile. No other neonatal outcome variables varied significantly between the UV flow rate centile groups.

	Overall	UV flow rate <10th Centile	UV flow rate 10th-90th Centile	UV flow rate >90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	2997 (2482 – 3630)	3448 (2440 – 4566)	3674 (3140 – 4080)	<0.001	n/a
Median Birthweight centile	45.0 (2 – 100)	21.0 (2 – 63)	42.0 (2 – 100)	67.0 (20 – 92)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	9.1% (1/11)	7.5% (7/93)	9.1% (1/11)	0.97	1.00 95% CI 0.07 – 14.05
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	27.3% (3/11)	21.5% (20/93)	27.3% (3/11)	0.88	1.00 95% CI 0.26 – 3.91
Incidence Base Excess < -8	16.5% (19/115)	0.0% (0/11)	18.3% (17/93)	18.2% (2/11)	0.37	n/a
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/11)	0.0% (0/93)	0.0% (0/11)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.45 (0 – 2)	0.53 (0 – 4)	0.64 (0 – 3)	0.78	n/a

Table 81. Comparison of neonatal outcome variables between UV flow rate centile groups

Relationship between neonatal outcome variables and corrected umbilical venous flow rate

None of the neonatal outcome variables had significant variation between the corrected UV flow rate centile groups (Table 80).

	Overall	Corrected UV flow rate <10th Centile	Corrected UV flow rate 10th-90th Centile	Corrected UV flow rate >90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	3394 (2510 – 3950)	3448 (2440 – 4566)	3277 (2580 – 3860)	0.41	n/a
Median Birthweight centile	45.0 (2 – 100)	48.0 (2 – 84)	42.0 (2 – 100)	46.0 (2 – 79)	0.94	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	0.0% (0/11)	9.7% (9/93)	0.0% (0/11)	0.34	n/a
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	36.4% (4/11)	20.4% (19/93)	27.3% (3/11)	0.54	1.33 95% CI 0.39 – 4.62
Incidence Base Excess < -8	16.5% (19/115)	18.2% (2/11)	16.1% (15/93)	18.2% (2/11)	0.98	1.00 95% CI 0.17 – 5.89
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/11)	0.0% (0/93)	0.0% (0/11)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.55 (0 – 2)	0.53 (0 – 4)	0.55 (0 – 3)	0.97	n/a

Table 82. Comparison of neonatal outcome variables between corrected UV flow rate centile groups

Relationship between neonatal outcome variables and amniotic fluid volume

None of the neonatal outcome variables had significant variation between the amniotic fluid index centile groups (Table 81).

	Overall	AFI <10th Centile	AFI 10th-90th Centile	AFI >90th Centile	ANOVA/ X^2 p=	Relative risk <10th centile vs. >90th centile
Mean Birthweight (g)	3426 (2440 – 4566)	3476 (3040 – 4320)	3426 (2440 – 4566)	3380 (2720 – 3836)	0.86	n/a
Median Birthweight centile	45.0 (2 – 100)	42.0 (16 – 97)	45.0 (2 – 100)	55.0 (4 – 78)	0.97	n/a
Incidence Apgar <7 at 1 min	7.8% (9/115)	0.0% (0/11)	8.6% (8/93)	(1/11)	0.62	n/a
Incidence Apgar <7 at 5 min	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence Cord arterial pH < 7.20	22.6% (26/115)	9.1% (1/11)	24.7% (23/93)	18.2% (2/11)	0.56	0.5 95% CI 0.05 – 4.75
Incidence Base Excess < -8	16.5% (19/115)	18.2% (2/11)	16.1% (15/93)	18.2% (2/11)	0.98	1.00 95% CI 0.17 – 5.89
Incidence of neonatal unit admission	0.9% (1/115)	0.0% (0/11)	1.1% (1/93)	0.0% (0/11)	0.89	n/a
Incidence of neonatal encephalopathy	0.0% (0/115)	0.0% (0/11)	0.0% (0/93)	0.0% (0/11)	n/a	n/a
Mean Composite neonatal outcome score	0.53 (0.0 – 4.0)	0.36 (0 – 3)	0.56 (0 – 4)	0.45 (0 – 1)	0.56	n/a

Table 83. Comparison of neonatal outcome variables between AFI centile groups

Discussion

In contrast to the findings from the early labour phase of the study, none of the ultrasound markers measured at 35 - 37 weeks gestation had significant variation between the different mode of delivery groups. These parameters also had no correlation with either the intra-partum or neonatal outcome variables. Whilst the study population was small, emergent trends that were apparent in the early labour pilot study (which had a similar population size), were noticeably absent from this cohort. However, this study population does not have sufficient power to conclude that ultrasound parameters measured between 35 and 37 weeks gestation are not predictive of intra-partum and neonatal outcomes. To power such a study would require 3200 cases to be recruited (based on the pilot data described here, assuming a significance level of 0.05, and based on an incidence of caesarean section for presumed fetal compromise of 18% in cases with a C/U ratio <10th centile, and 10% in cases with a C/U ratio >90th centile). The recruitment of such a large number of cases was unfortunately not possible within the time available.

Mean/median values for each ultrasound parameter measured at this gestation were consistent with those of published reference ranges[185, 233, 241].

This small study, conducted between 35 and 37 weeks gestation did not identify the differences in placental function, between babies at high and low risk of compromise in labour, that were observed in term babies in the previous chapter. This may be because in appropriately grown babies, it is deterioration in placental function late in the third trimester that subsequently precipitates intra-partum fetal compromise. Should this be the case, abnormalities will not be present when assessed at earlier gestations, at which time the deterioration in function is yet to occur. It is possible that pregnancies affected by intra-partum compromise undergo a more significant reduction in placental function than those where the fetus tolerates labour well. As such, the pathophysiology of intra-partum fetal compromise may be akin to that of late onset fetal growth restriction, which has been reported to be associated with different placental pathology to that of early onset growth restriction[380]. Link et al, have previously reported that a reduction in umbilical venous blood flow (corrected for fetal weight) in the third trimester may contribute to an “adverse intrauterine environment”[381]. Good placental function throughout the first and second trimesters, with a subsequent decline in the late third trimester, may not lead to a growth restricted/SGA fetus, as an adequate birthweight could already have been reached, but

could manifest as an inability of the fetus to tolerate the stresses of labour. This reduction in placental function and the concept of placental ageing has also been suggested as a possible causative mechanism in unexplained stillbirth[382], which may itself be the result of a more pronounced reduction in placental function. Accelerated placental maturation is also linked with both fetal growth restriction and pre-eclampsia[383]. Mckenna et al examined the relationship between a Grannum grade III placenta at 36 weeks gestation and subsequent pregnancy outcome[384]. The authors observed a significantly higher incidence of low birthweight in cases where the placenta displayed a greater degree of maturity. They also observed a higher rate of CTG abnormalities (19% vs. 12%). While this difference did not reach statistical significance, the study was relatively small, including only 68 cases with a Grade III placenta. An earlier, but larger study, did find a significant relationship between a Grade III placenta at 34-36 weeks and subsequent fetal compromise in labour[385]. Published longitudinal reference ranges for the C/U ratio report a degree of cerebral redistribution towards term gestation in all pregnancies[241], suggesting a gradual decline in placental function. It is possible that a longitudinal assessment of fetal Dopplers between 36 weeks gestation and term may be more informative of the risk of intra-partum fetal compromise than a single scan at either gestation.

Summary

This pilot study was undertaken to determine whether ultrasound assessments at earlier gestations would be more predictive of intra-partum fetal compromise than those undertaken at term. The data does not support a strong relationship between ultrasound assessment between 35 and 37 weeks gestation and subsequent intra-partum fetal compromise. However, the study population reported here was not sufficiently powered to definitively refute the null hypothesis. The pilot data collected will enable accurate power calculation for a larger study. The data reported here does suggest that the relationship between ultrasound parameters measured between 35 and 37 weeks gestation and intra-partum fetal compromise is unlikely to be as strong as that for ultrasound parameters measured at term. Further evaluation with a larger study population is required to confirm these findings.

Chapter 5 – Relationship between biomarkers of placental function (PAPP-A and B-HCG) and intra-partum/neonatal outcomes

Introduction

Evaluation of the synthetic function of the placenta in the first trimester has been used for the prediction of fetal anomalies[386] and of fetal growth restriction[281]. More recently, reduced PAPP-A levels have also been associated with an increased risk of intra-partum fetal compromise and emergency delivery[286]. The large cohort of patients recruited to the early labour phase of this project provided an opportunity to investigate the relationship between first trimester placental synthetic function and subsequent intra-partum compromise within an appropriately grown low risk cohort of pregnancies. It also provided the opportunity to correlate ultrasound finding at term with these markers.

Aim

To correlate first trimester maternal serum B-HCG and PAPP-A levels with intra-partum fetal compromise and fetal haemodynamics at term.

Methods

All women booked at Queen Charlotte's and Chelsea Hospital are offered first trimester screening using the combined test (B-HCG, PAPP-A, and nuchal translucency)[387]. All 604 cases recruited to the early labour phase were therefore considered eligible for inclusion. Case notes, electronic records, and printed serum screening results from the analysing laboratory were reviewed and B-HCG and PAPP-A levels, as well as multiple of the median (MoM) for the gestation at the time of sampling, were documented.

Following delivery, B-HCG and PAPP-A levels were correlated with mode of delivery, intra-partum and neonatal outcomes, and with ultrasound markers of fetal wellbeing.

Data Analysis

B-HCG and PAPP-A values were compared between the different mode of delivery groups using the Kruskal-Wallis test. The Kruskal-Wallis test, Mann Whitney test, and Spearman correlation co-efficient were used to evaluate the relationship between B-HCG/PAPP-A values and intra-partum and neonatal outcomes. Spearman correlation co-efficients were used to evaluate the relationship between B-HCG/PAPP-A values and ultrasound parameters.

Results

BHCG and PAPP-A levels were retrieved for 70.7% (427/604) of cases. In the remaining 177 cases, no BHCG and PAPP-A levels could be found. In 59 cases, a nuchal translucency was documented, but no serum screening results were present in any of the searched sources. In 38 cases women had declined serum screening, 25 cases were 'late booking' patients, for whom serum screening had been conducted at another institution and results were not traceable. Twenty seven cases had screening using the Quadruple test, and in 28 cases no reason for the absence of serum screening results was identified. All these cases were therefore excluded from further analysis, resulting in a study population of 427 cases.

Intra-partum fetal compromise necessitating emergency caesarean delivery occurred in 11.7% of the study population (50/427), whilst instrumental delivery for presumed fetal compromise occurred in 18.5% (79/427) of cases. Spontaneous vaginal deliveries were achieved in 39.8% (170/427) of cases, instrumental delivery for a prolonged 2nd stage in 14.8% (63/427) and emergency caesarean 'other' in 15.2% (65/427).

The median B-HCG was 42.1 (range 6.2 – 651.2) with a median MoM of 1.07 (range 0.19 – 8.80). Both B-HCG and B-HCG MoM had a non-normal distribution within the study population (Skewness = 6.17, Kurtosis = 59.75, D'agostino-Pearson p = <0.001 and Skewness = 3.34, Kurtosis = 18.73, D'agostino-Pearson p = <0.001 respectively).

The median PAPP-A was 3059 (range 316 – 55147) with a median MoM of 1.10 (range 0.17 – 4.33). Both PAPP-A and PAPP-A MoM had a non-normal distribution in the study population (Skewness = 9.24, Kurtosis = 136.4, D'agostino-Pearson p = <0.001 and Skewness = 1.28, Kurtosis = 2.40, D'agostino-Pearson p = <0.001 respectively).

Values were compared between the different mode of delivery groups (Table 82). No significant variation in B-HCG/B-HCG MoM or PAPP-A/PAPP-A MoM and subsequent mode of delivery was observed. Furthermore there was no significant variation in the ratio of B-HCG MoM to PAPP-A MoM between the mode of delivery groups. Dunn's multiple comparison testing confirmed that no two mode of delivery groups differed significantly from one another.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal-Wallis
Number of Patients	427	50	79	170	63	65	p =
B-HCG	42.1 (6.2 – 651.2)	43.9 (13.8 – 344.5)	37.6 (12.5 – 93.1)	42.8 (6.2 – 651.2)	41.0 (17.4 – 152.9)	46.1 (15.0 – 353.2)	0.53
B-HCG MoM	1.07 (0.19 – 8.80)	1.07 (0.39 – 8.8)	1.03 (0.35 – 2.64)	1.06 (0.19 – 7.41)	1.10 (0.54 – 3.82)	1.03 (0.35 – 6.44)	0.64
PAPP-A	3059 (316 – 55147)	3088 (316 – 10831)	3369 (522 – 8666)	2647 (323 – 55147)	3192 (626 – 12836)	3167 (690.5 – 7882)	0.10
PAPP-A MoM	1.10 (0.17 – 4.33)	1.15 (0.17 – 3.15)	1.07 (0.25 – 3.10)	1.00 (0.28 – 3.09)	1.19 (0.29 – 4.33)	1.19 (0.38 – 2.98)	0.19
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.55 (0.27 – 12.39)	1.16 (0.14 – 3.32)	1.52 (.21 – 10.65)	1.22 (0.21 – 3.06)	1.36 (0.21 – 8.98)	0.21

Table 84. BHCG and PAPP-A values according to mode of delivery group

Intra-partum outcomes

The relationship of B-HCG and PAPP-A values with intra-partum outcomes was also evaluated. B-HCG/B-HCG MoM, PAPP-A/PAPP-A MoM, and the B-HCG MoM/PAPP-A MoM ratio had no significant variation between the FHR classification groups (Table 83).

	Overall	Normal	Suspicious	Pathological	Kruskal-Wallis
Number of Patients	427	147	195	85	p =
B-HCG	42.1 (6.2 – 651.2)	44.3 (13.7 – 651.2)	41.0 (6.2 – 353.2)	42.1 (12.5 – 130.0)	0.73
B-HCG MoM	1.07 (0.19 – 8.80)	1.11 (0.35 – 6.44)	1.02 (0.19 – 8.80)	1.03 (0.39 – 3.48)	0.66
PAPP-A	3059 (316 – 55147)	2745 (323 – 10514)	3046 (316 – 55147)	3330 (884 – 10831)	0.30
PAPP-A MoM	1.10 (0.17 – 4.33)	1.13 (0.30 – 4.33)	1.08 (0.17 – 3.80)	1.09 (0.44 – 3.15)	0.55
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.18 (0.21 – 8.98)	1.46 (0.14 – 12.39)	1.23 (0.27 – 5.70)	0.41

Table 85. BHCG and PAPP-A values according to intra-partum monitoring group

Similarly, no significant variation was observed between cases with and without meconium stained liquor during labour (Table 84).

	Overall	Clear Liquor	Meconium stained Liquor	Mann Whitney
Number of Patients	427	378	49	p =
B-HCG	42.1 (6.2 – 651.2)	41.8 (6.2 – 651.2)	43.9 (19.8 – 130.0)	0.40
B-HCG MoM	1.07 (0.19 – 8.80)	1.07 (0.19 – 8.80)	1.10 (0.51 – 3.48)	0.48
PAPP-A	3059 (316 – 55147)	3039 (316 – 55150)	3188 (771 – 12840)	0.68
PAPP-A MoM	1.10 (0.17 – 4.33)	1.10 (0.17 – 4.33)	1.10 (0.44 – 3.10)	0.70
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.36 (0.14 – 12.39)	1.33 (0.21 – 5.70)	0.76

Table 86. BHCG and PAPP-A values according to liquor status

Neonatal outcome variables

The relationship between B-HCG and PAPP-A levels and neonatal outcomes was also investigated (Table 85).

No significant variations in B-HCG and PAPP-A levels were observed between infants with an Apgar score <7 at 1 minute of age and those with an Apgar score of 7 or more at 1 minute of age.

	Overall	Apgar score <7	Apgar score ≥7	Mann Whitney
Number of Patients	427	37	390	p =
B-HCG	42.1 (6.2 – 651.2)	39.2 (16.8 – 651.2)	43.0 (6.2 – 353.2)	0.35
B-HCG MoM	1.07 (0.19 – 8.80)	1.00 (0.35 – 3.16)	1.07 (0.19 – 8.80)	0.24
PAPP-A	3059 (316 – 55147)	3020 (796 – 10790)	3076 (316 – 55150)	0.86
PAPP-A MoM	1.10 (0.17 – 4.33)	1.10 (0.36 – 2.66)	1.10 (0.17 – 4.33)	0.84
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.09 (0.31 – 2.87)	1.42 (0.14 – 12.39)	0.16

Table 87. BHCG and PAPP-A values according to 1 minute Apgar score

No significant correlation between B-HCG/PAPP-A levels and birthweight were observed (Table 86).

Correlation	Spearman co-efficient
B-HCG and birthweight	-0.02 (p = 0.62)
B-HCG MoM and birthweight	-0.007 (p = 0.88)
PAPP-A and birthweight	-0.01 (p = 0.78)
PAPP-A MoM and birthweight	0.07 (p = 0.15)
B-HCG MoM/PAPP-A MoM ratio and birthweight	0.08 (p = 0.10)

Table 88. B-HCG/PAPP-A correlation with birthweight

No significant correlation between B-HCG/PAPP-A levels and birthweight centile were observed (Table 87).

Correlation	Spearman co-efficient
B-HCG and birthweight centile	-0.02 (p = 0.62)
B-HCG MoM and birthweight centile	-0.007 (p = 0.88)
PAPP-A and birthweight centile	-0.03 (p = 0.57)
PAPP-A MoM and birthweight centile	0.07 (p = 0.16)
B-HCG MoM/PAPP-A MoM ratio and birthweight centile	0.08 (p = 0.10)

Table 89. B-HCG/PAPP-A correlation with birthweight centile

B-HCG and PAPP-A levels were compared between infants with umbilical artery pH values at delivery of <7.20 and ≥7.20 (Table 88). PAPP-A levels were observed to be higher in cases with an umbilical artery pH at delivery of <7.20, but this difference was not present when PAPP-A MoM were compared.

	Overall	pH <7.20	pH ≥7.20	Mann Whitney
Number of Patients	427	142	285	
B-HCG	42.1 (6.2 – 651.2)	46.4 (6.2 – 275.4)	41.0 (7.5 – 651.2)	0.32
B-HCG MoM	1.07 (0.19 – 8.80)	1.10 (0.40 – 6.44)	1.03 (0.19 – 8.80)	0.13
PAPP-A	3059 (316 – 55147)	3200 (710 – 55150)	2895 (285 – 16910)	0.04
PAPP-A MoM	1.10 (0.17 – 4.33)	1.08 (0.28 – 2.93)	1.11 (0.17 – 4.33)	0.67
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.21 (0.21 – 5.63)	1.48 (0.14 – 12.39)	0.09

Table 90. BHCG and PAPP-A values according to umbilical artery pH at delivery

B-HCG and PAPP-A levels were compared between infants with umbilical artery base excess values ≥-8.0 and <-8.0 (Table 89). No significant differences were observed.

	Overall	Base excess ≥-8	Base excess <-8	Mann Whitney
Number of Patients	427	316	111	
B-HCG	42.1 (6.2 – 651.2)	41.7 (7.5 – 651.2)	44.9 (6.2 – 160.6)	0.39
B-HCG MoM	1.07 (0.19 – 8.80)	1.06 (0.19 – 8.80)	1.07 (0.45 – 3.23)	0.31
PAPP-A	3059 (316 – 55147)	3003 (316 – 12840)	3208 (323 – 55150)	0.26
PAPP-A MoM	1.10 (0.17 – 4.33)	1.12 (0.17 – 3.80)	1.05 (0.28 – 4.33)	0.66
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.40 (0.14 – 12.39)	1.36 (0.26 – 5.92)	0.77

Table 91 BHCG and PAPP-A values according to umbilical artery base excess at delivery.

B-HCG and PAPP-A levels were also compared between infants requiring neonatal unit admission and those that did not (Table 90). No significant variation was observed.

	Overall	Not admitted to NNU	Admitted to NNU	Mann Whitney
Number of Patients	427	420	7	
B-HCG	42.1 (6.2 – 651.2)	42.1 (6.2 – 651.2)	35.7 (16.9 – 78.5)	0.47
B-HCG MoM	1.07 (0.19 – 8.80)	1.07 (0.19 – 8.80)	0.83 (0.40 – 1.97)	0.34
PAPP-A	3059 (316 – 55147)	3095 (316 – 55150)	2599 (648 – 6101)	0.56
PAPP-A MoM	1.10 (0.17 – 4.33)	1.10 (0.17 – 4.33)	0.97 (0.55 – 2.66)	0.86
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.40 (0.14 – 12.39)	1.00 (0.41 – 2.35)	0.43

Table 92. BHCG and PAPP-A values according to requirement for neonatal unit admission

Finally, B-HCG and PAPP-A levels were correlated with the composite neonatal outcome score (Table 91). No significant variations were observed.

	Overall	0	1	2	3	4	>4	Kruskal-Wallis
Number of Patients	427	241	85	54	29	11	7	
B-HCG	42.1 (6.2 – 651.2)	41.0 (7.5 – 353.2)	43.5 (12.5 – 651.2)	40.4 (18.6 – 98.4)	57.8 (6.2 – 160.6)	36.4 (21.0 – 107.8)	30.3 (16.9 – 52.1)	0.08
B-HCG MoM	1.07 (0.19 – 8.80)	1.03 (0.19 – 8.80)	1.08 (0..35 – 6.44)	1.06 (0.54 – 2.64)	1.50 (0.45 – 3.23)	1.10 (0.54 – 2.28)	0.81 (0.40 – 1.39)	0.07
PAPP-A	3059 (316 – 55147)	2824 (316 – 12836)	3458 (323 – 16905)	3399 (710 – 10785)	2312 (995 – 55147)	2988 (1631 – 9419)	2599 (1473 – 5137)	0.22
PAPP-A MoM	1.10 (0.17 – 4.33)	1.12 (0.17 – 3.80)	1.13 (0.36 – 4.33)	1.05 (0.28 – 2.65)	0.95 (0.38 – 2.66)	1.21 (0.55 – 2.22)	1.18 (0.61 – 1.38)	0.63
B-HCG MoM/PAPP-A MoM ratio	1.39 (0.14 – 12.39	1.46 (0.14 – 12.39)	1.27 (0.28 – 8.82)	1.34 (0.31 – 4.80)	1.60 (0.30 – 3.99)	0.94 (0.44 – 1.88)	0.86 (0.41 – 1.74)	0.47

Table 93. BHCG and PAPP-A values according to composite neonatal outcome score

Relationship between 1st trimester BHCG/PAPP-A and ultrasound parameters

The association between 1st trimester levels of B-HCG/PAPP-A and ultrasound parameters from the early labour cohort were investigated.

Umbilical artery PI

No significant correlation between B-HCG/PAPP-A values and UA PI were observed within the study population (Table 92).

Correlation	Spearman co-efficient
B-HCG and UA PI	0.02 (p = 0.71)
B-HCG MoM and UA PI	0.006 (p = 0.90)
PAPP-A and UA PI	-0.03 (p = 0.58)
PAPP-A MoM and UA PI	-0.03 (p = 0.42)
B-HCG MoM/PAPP-A MoM ratio and UA PI	0.02 (p = 0.65)

Table 94. Correlation co-efficients of B-HCG/PAPP-A values and umbilical artery PI

Middle cerebral artery PI

No significant correlation between B-HCG/PAPP-A values and MCA PI were observed within the study population (Table 93).

Correlation	Spearman co-efficient
B-HCG and MCA PI	0.09 (p = 0.07)
B-HCG MoM and MCA PI	0.07 (p = 0.13)
PAPP-A and MCA PI	0.02 (p = 0.62)
PAPP-A MoM and MCA PI	0.01 (p = 0.79)
B-HCG MoM/PAPP-A MoM ratio and MCA PI	0.07 (p = 0.17)

Table 95. Correlation co-efficients of B-HCG/PAPP-A values and middle cerebral artery PI

Cerebro-umbilical ratio

No significant correlation between B-HCG/PAPP-A values and the cerebro-umbilical ratio were observed within the study population (Table 94).

Correlation	Spearman co-efficient
B-HCG and C/U ratio	0.03 (p = 0.49)
B-HCG MoM and C/U ratio	0.03 (p = 0.51)
PAPP-A and C/U ratio	0.02 (p = 0.65)
PAPP-A MoM and C/U ratio	0.03 (p = 0.48)
B-HCG MoM/PAPP-A MoM ratio and C/U ratio	0.03 (p = 0.60)

Table 96. Correlation co-efficients of B-HCG/PAPP-A values and the cerebro-umbilical ratio

Umbilical venous flow rate

A weak positive correlation between B-HCG MoM and UV flow rate was observed (Table 95). No other significant correlations between B-HCG/PAPP-A values and UV flow rate were observed within the study population.

Correlation	Spearman co-efficient
B-HCG and UV flow rate	0.07 (p = 0.12)
B-HCG MoM and UV flow rate	0.10 (p = 0.04)
PAPP-A and UV flow rate	0.01 (p = 0.77)
PAPP-A MoM and UV flow rate	0.03 (p = 0.60)
B-HCG MoM/PAPP-A MoM ratio and UV flow rate	0.05 (p = 0.36)

Table 97. Correlation co-efficients of B-HCG/PAPP-A values and umbilical venous flow rate

Corrected umbilical venous flow rate

A weak positive correlation between B-HCG and B-HCG MoM and corrected UV flow rate was observed (Table 96). No significant correlation between PAPP-A values and corrected UV flow rate were observed within the study population. The weak positive correlation between the B-HCG MoM/PAPP-A MoM ratio and corrected UV flow bordered significance.

Correlation	Spearman co-efficient
B-HCG and corrected UV flow rate	0.11 (p = 0.03)
B-HCG MoM and corrected UV flow rate	0.12 (p = 0.01)
PAPP-A and corrected UV flow rate	0.03 (p = 0.53)
PAPP-A MoM and corrected UV flow rate	0.01 (p = 0.80)
B-HCG MoM/PAPP-A MoM ratio and corrected UV flow rate	0.09 (0.05)

Table 98. Correlation co-efficients of B-HCG/PAPP-A values and corrected umbilical venous flow rate

Uterine artery PI

A weak negative correlation between PAPP-A and PAPP-A MoM and uterine artery PI was observed (Table 97). No significant correlation between B-HCG values and uterine artery PI were observed within the study population.

Correlation	Spearman co-efficient
B-HCG and uterine artery PI	-0.09 (p = 0.12)
B-HCG MoM and uterine artery PI	-0.09 (p = 0.10)
PAPP-A and uterine artery PI	-0.11 (0.05)
PAPP-A MoM and uterine artery PI	-0.11 (p = 0.04)
B-HCG/PAPP-A ratio and uterine artery PI	0.003 (p = 0.95

Table 99. Correlation co-efficients of B-HCG/PAPP-A values and uterine artery PI

Amniotic fluid volume

No significant correlation between B-HCG values and amniotic fluid index were observed within the study population (Table 98). Both PAPP-A and PAPP-A MoM had a weak negative correlation with amniotic fluid index, whilst the B-HCG MoM/PAPP-A MoM ratio had a weak positive correlation.

Correlation	Spearman co-efficient
B-HCG and AFI	0.00 (p = 0.98)
B-HCG MoM and AFI	0.02 (p = 0.66)
PAPP-A and AFI	-0.14 (p = 0.003)
PAPP-A MoM and AFI	-0.13 (p = 0.009)
B-HCG/PAPP-A ratio	0.11 (p = 0.03)

Table 100. Correlation co-efficients of B-HCG/PAPP-A values and amniotic fluid index.

Discussion

Measurement of placental derived proteins B-HCG and PAPP-A are primarily used in 1st trimester screening for chromosomal anomalies[388]. However, many studies have also reported the relationship between 1st trimester B-HCG and PAPP-A levels, and subsequent adverse pregnancy outcomes[292, 389, 390]. As both B-HCG and PAPP-A are produced by the placenta, they may be considered measures of placental function. Other investigators have also assessed the correlation between first trimester PAPP-A and B-HCG levels and subsequent fetal compromise during labour[286, 294].

Within the study population, both B-HCG and PAPP-A were found to have non-normal distributions. In a similar manner to the non-normal distributions observed for many of the ultrasound parameters measured in early labour, it is possible that the exclusion of any pregnancies with evidence of placental dysfunction may have resulted in the non-normal distribution.

Having evaluated 1st trimester B-HCG and PAPP-A levels from 427 normal pregnancies, no significant variation between the mode of delivery groups for either absolute values of these markers or gestation controlled multiples of the median (MoM) levels were identified. Similarly no significant variation was observed between the intra-partum or neonatal outcome groups. These findings are in contrast to those of other published studies[286, 294].

PAPP-A

Uccella et al[286], evaluated the relationship between PAPP-A levels and subsequent intra-partum outcomes, and found that low PAPP-A was significantly associated with caesarean delivery for presumed fetal compromise. A number of methodological differences may explain the disparity between the findings of Uccella et al, and those from the current study. Uccella et al prospectively recruited cases with a PAPP-A level <0.52 MoM and compared this group with those with a PAPP-A level >0.52 MoM. As PAPP-A levels below this cut off have been associated with both fetal growth restriction and pre-eclampsia[391], many cases with PAPP-A levels below this cut off would have been excluded from the current study. Furthermore, a proportion of cases in the Uccella study that delivered by caesarean delivery for presumed fetal compromise were also small for gestational age, and so may have been growth restricted, a potential confounding factor, although the authors multivariate analysis

did suggest an independent relationship between PAPP-A levels and subsequent intra-partum compromise. Further analysis of our data demonstrated an identical incidence of caesarean delivery for presumed fetal compromise in cases with a PAPP-A <0.52 MoM and those with a PAPP-A >0.52 MoM (11.7%). The current study was not designed to capture cases with low PAPP-A levels, and as a result there were only 34 cases with PAPP-A <0.52 in the study population. Few other studies have evaluated the association between 1st trimester PAPP-A levels and subsequent intra-partum outcomes. It is possible that a relationship does exist, but in a dose-dependent form, with very low 1st trimester levels required to predispose the fetus to subsequent intra-partum fetal compromise.

Results from the current study also found no significant correlation between birthweight or birthweight centile and 1st trimester PAPP-A levels. However, when birthweights and birthweight centiles for cases with PAPP-A <0.52 MoM and >0.52 MoM were compared, significantly lower birthweight and birthweight centile were found in the <0.52 MoM group ($p = 0.03$ and $p = 0.03$ respectively). These findings support the suggestion that the relationship between 1st trimester PAPP-A levels and placental function is not directly proportional, and that only very low levels of PAPP-A indicate a potential reduction in placental performance.

When 1st trimester PAPP-A levels were correlated with the early labour ultrasound parameters, few significant relationships were identified. A weak negative correlation was found between PAPP-A MoM and Uterine artery PI, and also between PAPP-A MoM and AFI. A negative correlation between Uterine artery PI and PAPP-A levels in the 1st trimester has been reported[392]. Increased uterine artery resistance is suggestive of sub-optimal placentation and adverse pregnancy outcomes[247], as is a reduction in 1st trimester PAPP-A levels. No significant variation in AFI was found between cases with PAPP-A <0.52 and those with PAPP-A >0.52. No published studies could be found examining the relationship between 1st trimester PAPP-A levels and AFI at term. Whilst these associations did reach statistical significance, the weakness of the correlation mean they are possibly of limited clinical significance.

B-HCG

Obiekwe and Chard reported in 1982 that B-HCG levels could be correlated to the development of intra-partum fetal compromise[294], however no publications since this time have investigated this relationship. Whilst the current study investigated B-HCG levels measured during the 1st trimester, Obiekwe and Chard evaluated levels measured between 36 and 40 weeks gestation, a methodological difference that may be responsible for the disparity in results. Data from the current study does not support the existence of a relationship between B-HCG levels in the 1st trimester and subsequent intra-partum fetal compromise. A more recognised association is that of fetal growth restriction/SGA with low 1st trimester B-HCG levels. Kirkegaard et al[293] found that a B-HCG level < 0.5 MoM was associated with a significantly increased odds ratio for SGA. However, data from the current study did not demonstrate any significant correlation between birthweight or birthweight centile and 1st trimester B-HCG values. Further analysis of our data using a cut of B-HCG of 0.5 MoM failed to demonstrate significant variation in the incidence of caesarean delivery for presumed fetal compromise, or a difference in birthweight or birthweight centile. As the current study targeted recruitment of 'normal' pregnancy, the absence of an association between birthweight and B-HCG levels may be due to an insufficient number of low B-HCG cases within the study population. Only 21 cases were identified with a B-HCG level <0.5 MoM. The results of Kirkgaard et al demonstrate that the odds ratio for SGA increased as the cut off B-HCG level was reduced, with the strongest relationship identified when a cut off of <0.3 MoM was used. Only one case in the current study population was identified with a B-HCG level this low.

When the relationship between 1st trimester B-HCG levels and ultrasound parameters was examined, the only significant finding was a weak positive correlation between umbilical venous flow and corrected umbilical venous flow, and B-HCG MoM values. Whilst there is a paucity of published evidence directly describing the relationship between B-HCG and umbilical venous flow, there is a growing body of work demonstrating that abnormalities in ductus venosus flow (which is dependent on umbilical venous flow to a degree) is associated with chromosomal anomalies[393], which in turn are associated with abnormal B-HCG levels.

Summary

B-HCG and PAPP-A levels measured in the 1st trimester are not predictive of intra-partum fetal compromise within a 'normal' population. As already discussed in chapter 4, there is significant potential for placental function to deteriorate throughout pregnancy, and as a result it is perhaps unsurprising that measures of the placenta's synthetic function in the 1st trimester do not correlate with its performance at the end of pregnancy. The absence of an association between 1st trimester markers and subsequent intra-partum fetal compromise further supports the suggestion that intra-partum fetal compromise occurring in low risk pregnancy is precipitated by a gradual reduction in function of a previously adequate placenta, rather than the presence of a sub-optimally developed placenta secondary to impaired placentation.

Chapter 6 – Composite risk score

Introduction

Results from the early labour phase of the project demonstrated that UA PI, MCA PI, the C/U ratio, and umbilical venous flow, when measured in early labour, have significant variation between fetuses subsequently delivered by different modes of delivery. Division of cases into centile groups according to the values of each of these parameters, further demonstrated that they were predictive of subsequent signs of fetal compromise during labour. Whilst the C/U ratio was the most predictive measure when used independently and had excellent negative predictive value, its positive predictive value (when the C/U ratio was $<10^{th}$ centile) for subsequent caesarean delivery for presumed fetal compromise was only 36%.

Further investigations demonstrated that measurement of the same ultrasound parameters, at an earlier gestation (36 weeks), and the levels of the placental proteins, PAPP-A and B-HCG, measured during the 1^{st} trimester were not similarly predictive of subsequent mode of delivery, or the development of signs of intra-partum fetal compromise.

The most valuable markers of intra-partum fetal compromise identified during this project were therefore UA PI, MCA PI, the C/U ratio, and umbilical venous flow, measured in early labour. This chapter details the development of a composite risk score, from these variables, in an effort to increase the positive predictive value for subsequent intra-partum fetal compromise, and yet maintain the good negative predictive value that the C/U ratio offered when used in isolation.

Aims

1. To develop a composite risk score to predict intra-partum fetal compromise, using early labour UA PI, MCA PI, C/U ratio, and umbilical venous flow.

2. To correlate this composite risk score with subsequent intra-partum and neonatal outcomes.

Methods

Data from the early labour cohort was used for this phase of the study. As all cases required a full complement of Doppler parameters, two cases where data regarding umbilical venous flow rate was absent were excluded, resulting in a study population of 602 cases. Cases were divided quantitatively into three groups (<10th centile, 10th-90th centile, and >90th centile) based on the pulsatility index of each of the fetal vessels (and corrected flow rate in the case of the umbilical vein). Points (0-2) were awarded to each case for each Doppler parameter (Table 99), and then added together to calculate the composite risk score. The scoring mechanism was kept deliberately simplistic, to facilitate use by clinicians and other health care professionals at the bedside. The minimum number of points each case could accumulate was zero, whilst the maximum number of points was eight. Cases were then sub-classified according to the scores from all fetal vessels and intra-partum and neonatal outcomes compared.

	UA PI	MCA PI	C/U ratio	Corrected UV flow
<10th Centile	0	2	2	2
10th-90th Centile	1	1	1	1
>90th Centile	2	0	0	0

Table 101. Points' allocation

The primary outcomes for the study were mode of delivery, and the presence/absence of a diagnosis of intra-partum fetal compromise. Secondary outcomes included the intra-partum outcomes variables and neonatal outcome variables used in the early labour and 36 week gestation phases.

Data analysis

Composite risk score values were compared between the mode of delivery groups using Kruskal-Wallis and Dunn's multiple comparison testing. The incidence of intra-partum outcomes was compared between composite risk score groups using chi-squared testing and calculation of relative risks with 95% confidence intervals.

Results

Composite risk scores were calculated for 602 cases.

Umbilical artery

Within the study population the UA PI had a 10th centile value of 0.63 and a 90th centile value of 0.98. This resulted in 50 cases with a UA PI <10th centile, 494 cases with a UA PI 10th - 90th centile, and 58 cases with a UA PI >90th centile (see Table 99 for points allocation).

Middle cerebral artery

Within the study population the MCA PI had a 10th centile value of 1.03 and a 90th centile value of 1.72. This resulted in 54 cases with an MCA PI <10th centile, 494 cases with an MCA PI 10th – 90th centile, and 54 cases with an MCA PI >90th centile (see Table 99 for points allocation).

Cerebro-umbilical ratio

Within the study population the C/U ratio had a 10th centile value of 1.24 and a 90th centile value of 2.33. This resulted in 57 cases with a C/U ratio <10th centile, 487 cases with a C/U ratio 10th – 90th centile, and 58 cases with a C/U ratio >90th centile (see Table 99 for points' allocation).

Corrected Umbilical venous flow

Within the study population corrected umbilical venous flow had a 10th centile value of 41.1 ml/min/kg, and a 90th centile value of 79.2 ml/min/kg. This resulted in 60 cases with a corrected UV flow <10th centile, 482 cases with a corrected UV flow 10th – 90th centile, and 60 cases with UV flow >90th centile (see Table 99 for points' allocation).

The accumulated composite risk score had a non-normal distribution (D'agostino-Pearson p = <0.001), with a median value of 4 (range 0 – 8). The non-normal distribution occurred secondary to kurtosis (1.4) as opposed to skewness (0.04), and as a result the mean is still considered representative of the distribution.

The accumulated score was then compared between infants in each mode of delivery group (Table 100). Infants born by emergency caesarean section for presumed fetal compromise had the highest mean score (4.6, range 2-8), whilst infants born by instrumental delivery for

a prolonged 2nd stage had the lowest mean score (3.8, range 0-6). Infants born by SVD had a mean score of 3.9 (range 1-7), and those born by instrumental delivery for presumed fetal compromise had a mean score of 4.2 (range 1-7). The difference in score between the different mode of delivery groups was significant (p=<0.001). Dunn's multiple comparison testing confirmed that the mean composite risk score in cases delivered by caesarean for presumed fetal compromise was significantly different to all other mode of delivery groups, except cases delivered by instrumental for presumed fetal compromise.

	Overall	Emergency LSCS FD	Instrumental FD	SVD	Instrumental FTP	Emergency LSCS other	Kruskal Wallis
Number of Patients	602	69	110	237	96	90	
Composite risk score	4.0 (0 – 8)	4.6 (2 – 8)	4.2 (1 – 7)	3.9 (1 – 7)	3.8 (0 – 6)	3.9 (1 – 7)	<0.001

Table 102. Composite risk score according to mode of delivery group

Cases were then grouped according to their accumulated score from all fetal vessels (Table 101). Fifteen cases had a composite risk score of 7-8, 121 cases had a score of 5-6, 412 cases had a score of 3-4, and 54 cases had a score of 0-2. Mode of delivery outcomes were compared between these composite risk score groups. Fetuses with the highest scores (7 or 8) had the highest incidence of emergency caesarean delivery for presumed fetal compromise, with an incidence of 53.3% seen in this group. In comparison, fetuses with the lowest scores (0-2) had an incidence of caesarean delivery for presumed fetal compromise of just 3.7%. When compared to fetuses with the lowest scores, those with the highest scores were at increased risk of caesarean delivery for presumed fetal compromise, with a relative risk of over 14. These fetuses were also more likely to be diagnosed with fetal compromise during the labour and were less likely to be born vaginally (either instrumental or spontaneous vaginal delivery).

Delivery category	Overall	Composite score 0-2	Composite score 3-4	Composite score 5-6	Composite score 7-8	X^2p=	Relative risk 0-2 and 7-8
Caesarean section for Fetal compromise	11.5% (69/602)	3.7% (2/54)	9.7% (40/412)	15.7% (19/121)	53.3% (8/15)	<0.001	14.40 95% CI 3.41 – 60.78
Fetal compromise diagnosed at any time during labour	29.7% (179/602)	16.7% (9/54)	27.7% (114/412)	36.4% (44/121)	80.0% (12/15)	<0.001	4.80 95% CI 2.51 – 9.17
SVD	39.4% (237/602)	53.7% (29/54)	38.1% (157/412)	40.5% (49/121)	13.3% (2/15)	0.13	0.25 95% CI 0.07 – 0.92
Vaginal delivery of any kind	73.6% (443/602)	85.2% (46/54)	74.0% (305/412)	71.1% (86/121)	40.0% (6/15)	0.33	0.47 95% CI 0.25 – 0.88
Caesarean section for other indication	15.0% (90/602)	11.1% (6/54)	16.3% (67/412)	13.2% (16/121)	6.7% (1/15)	0.59	0.60 95% CI 0.08 – 4.61

Table 103. Delivery outcomes according to composite risk score group

Maternal demographic parameters were compared between the four different risk score groups. Significant variation was found only in the gestation at onset of labour, which was lower (40.1 weeks) in the lowest scoring group than in the other groups (40.5, 40.7, and 40.5 weeks).

Intra-partum outcomes

The intra-partum outcome variables were compared between the different composite risk score groups (Table 102). Significant variation in the incidence of pathological intra-partum monitoring was observed. Compared to those with the lowest composite risk scores, cases with the highest risk scores were almost five times more likely to subsequently develop pathological fetal heart rate patterns during labour. No significant variation in the incidence of either suspicious intra-partum monitoring or meconium stained liquor was observed between the risk score groups.

	Overall	Score 0 - 2	Score 3 - 4	Score 5 - 6	Score 7 - 8	X^2p=	Relative risk 0 - 2 vs. 7 – 8
CTG abnormalities - Pathological	19.8% (119/602)	11.1% (6/54)	19.2% (79/412)	21.5% (26/121)	53.3% (8/15)	<0.001	4.80 95% CI 1.97 – 11.70
CTG abnormalities - Suspicious	45.5% (274/602)	44.4% (24/54)	44.7% (184/412)	49.6% (60/121)	40.0% (6/15)	0.56	0.90 95% CI 0.45 – 1.79
Meconium stained liquor	12.5% (75/602)	13.0% (7/54)	11.4% (47/412)	15.7% (19/121)	13.3% (2/15)	0.49	1.03 95% CI 0.24 – 4.45

Table 104. Intra-partum FHR classification and meconium status according to composite risk score group

Neonatal outcomes

Both birthweight and birthweight centile had significant variation between the different composite risk score groups. The group with the lowest risk score had the highest birthweight and the highest birthweight centile, whereas cases with the highest composite risk scores had the second lowest birthweight and the lowest birthweight centile.

No other significant variation in neonatal outcome variables was observed between the different composite risk score groups (Table 103).

	Overall	Score 0 - 2	Score 3 - 4	Score 5 - 6	Score 7 - 8	ANOVA/ X2 p=	Relative risk 0 – 2 vs. 7 – 8)
Mean Birth weight (g)	3530 (1780 – 5026)	3618 (2360 – 4470)	3559 (2390 – 5026)	3408 (1780 – 4858)	3415 (2676 – 4906)	0.005	n/a
Median Birth weight centile	53.5 (1 – 100)	61.0 (5 – 99)	55.5 (1 – 100)	43.0 (1 – 100)	23.0 (3 – 100)	<0.001	n/a
Incidence Apgar <7 at 1 min	7.5% (45/602)	11.1% (6/54)	7.5% (31/412)	6.6% (8/121)	0% (0/15)	0.53	n/a
Incidence Apgar <7 at 5 min	1.0% (6/602)	1.9% (1/54)	0.7% (3/412)	1.7% (2/121)	0% (0/15)	0.71	n/a
Incidence Cord arterial pH < 7·20	31.4% (189/602)	31.5% (17/54)	31.6% (130/412)	32.2% (39/121)	20.0% (3/15)	0.88	0.64 95% CI 0.21-1.88)
Incidence Base Excess < -8	24.3% (146/602)	27.8% (15/54)	24.0% (99/412)	25.6% (31/121)	6.7% (1/15)	0.51	0.24 95% CI (0.03 – 1.67)
Incidence of neonatal unit admission	1.5% (9/602)	3.7% (2/54)	0.7% (3/412)	3.3% (4/121)	0% (0/15)	0.10	n/a
Incidence of neonatal encephalopathy	0% (0/602)	0% (0/54)	0% (0/412)	0% (0/121)	0% (0/15)	n/a	n/a
Mean Composite neonatal outcome score	0.78 (0 – 7)	0.89 (0 – 5)	0.75 (0 – 5)	0.88 (0 – 7)	0.40 (0 – 4)	0.28	n/a

Table 105. Neonatal outcomes according to composite risk score group

Discussion

Results from the early labour phase of this project demonstrated that the UA PI, MCA PI, C/U ratio, and UV flow did vary significantly between fetuses subsequently born by different modes of delivery. However, whilst the negative predictive value, particularly of a high C/U ratio (NPV 98%) was good, their positive predictive value was relatively low (36%). The development of the composite risk score has demonstrated that by combining these parameters, the positive predictive value for caesarean delivery for presumed fetal compromise in the highest risk cases can be improved to over 50%, whilst largely maintaining the negative predictive value for fetuses with the lowest risk scores. In this study, fetuses with the highest risk scores were over 14 times more likely to require delivery by caesarean section for presumed fetal compromise, when compared to those with the lowest risk scores.

Significant variation in both birthweight and birthweight centile was also observed, with the largest infants found in the group with the lowest risk score. This difference cannot be accounted for by maternal demographics, as apart from gestation, no significant variation in maternal demographic characteristics was observed between the different risk score groups. Whilst the gestation of the lowest risk score group was significantly lower than that of the other groups, the absolute difference in gestation between the groups was small (0.6 weeks), and for this reason the difference in gestation is unlikely to have a confounding influence. Furthermore, an earlier gestation would be expected to result in a smaller birthweight, not the larger birthweights observed in the study population. The greater size of infants in the lowest risk score groups is suggestive that placental function is better in these pregnancies, resulting in a lower incidence of intra-partum compromise and emergency delivery. It is important to note however that risk stratification on the basis of estimated fetal weight alone would be unreliable. In the highest risk scoring group 93.3% (14/15) of babies had birth weights above the 10^{th} centile, a cut off generally used to define a small for gestational age fetus.

Whilst the use of the composite risk score was able to identify pregnancies at high and low risk of intra-partum fetal compromise, a significant limitation is that the majority of caesarean sections for presumed fetal compromise still took place in cases with risk scores outside the highest group. As a result whilst the scoring system described here is predictive of intra-partum fetal compromise, its predictive value is likely to be insufficient to enable its

use as a decision making tool regarding mode of delivery. It is likely that even a perfect assessment of placental function may have limited positive predictive value for intra-partum fetal compromise, as whilst such an assessment would determine how much 'stress' a fetus could tolerate during labour, in this regard not all labours are equal. Intrauterine pressures are known to be reduced in multiparous women, in whom rates of intra-partum fetal compromise are lower[69]. Fetuses exposed to increased levels of uterine activity during labour, are more likely to be acidotic at delivery[68]. The prediction of intra-partum fetal compromise, with an adequate positive predictive value to guide mode of delivery decisions prior to labour, is therefore likely to require not only an estimate of the fetuses ability to tolerate the stresses of labour, but also an estimate of the degree of stress it is required to endure in order to achieve a vaginal delivery.

Whilst the positive predictive value of this test may limit it's clinical utility, the extremely good negative predictive value of this technique, would lend itself to the identification of pregnancies suited to delivery away from a hospital setting.

No significant variation in neonatal outcome variables was observed between the different composite risk score groups.

Chapter 7 – Maternal Oxygen therapy

Introduction

The risk stratification of normal pregnancies prior to established labour, offers not only the opportunity for women to make more informed decisions about their mode and place of delivery, but also the opportunity to target therapies to those cases identified as high risk for intra-partum fetal compromise. Such therapies would aim to modify the risk profile of an individual fetus, reducing the likelihood of intra-partum fetal compromise, and the associated requirement for emergency operative delivery. The studies reported in this thesis have suggested that deterioration in placental function in the late third trimester may predispose some appropriately grown fetuses to intra-partum compromise. This reduction in placental function may limit the effective oxygenation of fetal blood during periods of stress, such as during labour. Fetuses at increased risk of intra-partum compromise share similar haemodynamic features with those affected by fetal growth restriction, a condition associated with chronic hypoxia[394].

The association of growth restriction and hypoxia

Lichty et al examined 'prematurity' rates amongst the counties of Colorado observing that the highest 'prematurity' rates were associated with populations residing at the greatest altitude, and that despite the difference in birthweight, there was no significant difference in gestational age between these babies and those born at sea level[395]. This difference was initially presumed secondary to maternal socio-demographic factors, but in 1997, Jensen and Moore suggested that high altitude residence was responsible for the increased incidence of low birthweight babies[396]. Similar associations were reported in other high altitude populations[397, 398], and the association between the reduced Oxygen tension in these environments and a reduction in birthweight was established[399].

The differing partial pressure of Oxygen in maternal and fetal blood is a critical regulator of Oxygen diffusion across the placental barrier[400]. At high altitudes, the lower Oxygen tension reduces the diffusion gradient and may impact the oxygenation of fetal blood. The reduced Oxygen tension also influences placental development. Uterine artery blood flow increases during pregnancy in order to improve fetal oxygenation[394]. However, this increase is tempered by high altitude residence[401], despite uterine artery resistance being

lower at altitude than at sea level during the first 25 weeks of pregnancy. There is also evidence that remodelling of spiral arteries, critical in establishing a low resistance circulation within the placenta, is reduced in women residing at altitude[402].

An association between hypoxia and a restriction in fetal growth is also suggested by several animal studies. De Grauw et al demonstrated that exposure of pregnant rats to hypoxic conditions led to a reduction in fetal weight[403], whilst a similar finding in sheep was observed by Jacobs et al[404]. Furthermore, studies of chick embryos have found that increasing atmospheric Oxygen content can ameliorate the growth retarding effects of altitude[405]. In humans, umbilical venous blood in growth restricted fetuses, sampled by cordocentesis prior to labour, has been found to have reduced Oxygen tensions when compared to appropriately grown babies[406]. Maternal hyper-oxygenation in cases of severe growth restriction does result in increased Oxygen tensions within the fetal circulation[407]. A Cochrane review conducted in 2003 examined three further trials investigating the use of maternal hyper-oxygenation to treat fetal growth restriction[408]. Studies by Battaglia et al[409], Johanson et al[410], and Lindow et al[411], all reported a reduction in perinatal mortality, but were confounded by a higher gestational age at delivery in the group of women receiving Oxygen therapy. A significant increase in birthweight was not reported.

Maternal Oxygen therapy and fetal compromise

Maternal Oxygen therapy is frequently employed during labour in an effort to improve Oxygenation of a compromised fetus. There are reports that maternal hyper-oxygenation can influence fetal wellbeing. In 1988, Leader and Baillie compared fetal movements in response to vibroacoustic stimulation (a test of fetal wellbeing[412]), finding that the incidence of a normal response was significantly reduced when mothers were asked to breathe a reduced concentration of inspired Oxygen[413]. Whilst some studies have reported benefit from maternal Oxygen therapy[414], others have suggested it may have a negative impact on the fetus via Oxygen mediated vasoconstriction of fetal vessels[415]. Thorp et al treated women with supplemental Oxygen during the second stages of labour, comparing umbilical cord pH to a control group[416]. Whilst they observed a statistically significant reduction in pH associated with Oxygen therapy, this reduction was not felt to be clinically significant. Furthermore, the study was confounded by the longer second stage experienced by babies in the Oxygen therapy group. A similar study performed in 1992 examined umbilical cord biochemistry after maternal Oxygen administration during elective caesarean

and found no significant differences between the Oxygen therapy and control groups[417]. However, Simpson and James demonstrated in 2005 that maternal Oxygen therapy does increase fetal Oxygen saturation, particularly in fetuses with saturations of less than 40%[418].

The impact of maternal oxygen therapy on the fetal heart rate is similarly contentious. Both Khazin et al[419] and Althabe et al[420] reported an improvement of pathological fetal heart rate patterns during maternal Oxygen administration. An increase in the number of accelerations has also been reported[421]. However, other authors have observed a reduction in fetal heart rate variability following maternal Oxygen administration[422].

There has been limited investigation of the impact of maternal hyper-oxygenation on feto-placental blood flow. An increase in the internal carotid artery PI was reported by Arduini et al[423], but subsequent reports demonstrated no effect on middle cerebral artery and umbilical artery resistance indices[424].

Safety of maternal Oxygen therapy

Maternal oxygen therapy is currently used routinely in obstetrics in a variety of settings. In many Obstetric units, women who develop acute fetal heart rate abnormalities during labour are treated empirically with high flow oxygen therapy in an attempt to improve fetal oxygenation. Women undergoing epidural insertion, where there is a risk of maternal hypotension (and subsequent fetal distress) following the procedure, are also given supplemental oxygen. Women with severe lung disease and/or cardiac disease may require long term supplemental oxygen for maternal reasons.

The potential issues concerning the safety of maternal Oxygen therapy include Oxygen induced vasoconstriction on the maternal side of the placenta[415, 425] and the production of Oxygen free radicals and lipid peroxidation. Jouppila et al observed that following maternal Oxygen therapy, intervillous blood flow on the maternal side of the placenta was reduced[425], however, no concomitant effect was observed on umbilical venous flow rates. Despite this potentially adverse effect, other investigators have not demonstrated a deleterious effect of Oxygen therapy on placental function or fetal wellbeing. Whilst Thorp et al did report lower umbilical artery pH in babies whose mothers received supplemental Oxygen[426], this difference was not clinically significant, and the study was confounded by the significantly longer second stage of labour found in the Oxygen therapy group[416].

Oxygen free radicals may be generated following both hypoxia and hyperoxia, and production may be compounded by a combination of both[426]. There is potential for such free radicals to interact with lipid cell membranes resulting in damage[427]. In ex-utero life, this has been suggested to exacerbate hypoxic ischaemic encephalopathy. Klinger et al examined outcomes of neonates with hypoxic ischaemic encephalopathy and found that babies exposed to extreme hyperoxia and hypocapnia in the first few hours of life had a greater incidence of adverse outcome[428]. Animal studies also suggest that maternal hyperoxia is associated with an increased production of free radical species in the fetus[429, 430]. However, in a randomised controlled trial in humans, Khaw et al found no evidence of increased lipid peroxidation in either mother or fetus, following maternal hyper-oxygenation during caesarean delivery[427].

Aim

To investigate the effect of maternal Oxygen therapy on feto-placental haemodynamics.

Methods

This self-controlled cohort study was undertaken between July 2013 and November 2013 at the Mater Mother's Hospital, Brisbane, Australia. The study protocol was reviewed and accepted by the Mater Research Ethics Committee (Reference no. HREC/13/MHS/99). All women at term with uncomplicated, singleton pregnancies, and likely to deliver within 72 hours were considered eligible for inclusion. Data from previous studies was used for power calculation. This suggested a power of >0.8 to demonstrate a change in the C/U ratio of 0.3 following maternal Oxygen therapy could be achieved with a sample size of 20 participants. The study was powered to demonstrate a change of 0.3 in the C/U ratio as data from previous studies suggested this would be sufficient to reduce the risk of intra-partum fetal compromise for babies with the lowest C/U ratios.

Potential participants were approached by a member of the research team prior to induction of labour, or in the latent phase of spontaneous labour (<4cm dilated). Women with a history suggestive of placental dysfunction, such as pre-eclampsia, or SGA/FGR were not eligible for inclusion. Participants were asked to read an information sheet (Appendix E), and given time to ask questions and have any concerns addressed prior to enrolment. Those happy to be included in the study were asked to sign a consent form (Appendix F). All participants then underwent an ultrasound scan, identical to those performed during the previous chapters of this thesis. After a 20 minute time period, a further ultrasound scan was performed (to act as a control for subsequent scans performed after Oxygen therapy), and all measurements, except fetal biometry were repeated. After completion of this ultrasound scan, participants were asked to breathe 60% Oxygen, through a facial mask. To ensure that all participants received the same concentration of inspired Oxygen, Venturi masks with adjustable ties were used to deliver an accurate Oxygen concentration and to achieve a close fit to the participant's nose and mouth. An inspired Oxygen concentration of 60% was chosen as this is the highest fixed concentration achievable with a Venturi mask. After 20 minutes, maternal Oxygen therapy was stopped, and a repeat ultrasound scan performed. One further scan was performed following another 20 minute period of breathing normal room air. Maternal Oxygen saturations were monitored throughout the procedure.

Fetal haemodynamics were then compared between the baseline scan performed at 0 minutes, and subsequent scans performed at 20, 40 and 60 minutes, using paired t-tests, correlation co-efficients.

Results

Twenty women were recruited to the study over a three week time period. Maternal demographics are documented in Table 104.

	Overall
Number of Patients	20
% Nulliparous	70.0% (14/20)
Mean Maternal Age (years)	28.8 (16 – 37)
Mean BMI (kg/m^2)	26.6 (21 – 32)
Mean gestation (weeks)	40.3 (38.0 – 14.4)
Ethnicity (%)	
Caucasian	(15/20)
Asian	(4/20)
Afro-Caribbean	(0/20)
Other	(1/20)
Mode of onset of labour (%)	
Induction	80.0% (16/20)
Spontaneous	20.0% (4/20)

Table 106. Maternal demographics and mode of onset of labour

The UA PI, MCA PI, C/U ratio, UV flow, and uterine artery PI were compared between time points using paired t-tests (Table 105). Only MCA PI varied significantly between assessment before and after maternal Oxygen therapy (1.37 vs. 1.35). Whilst this variation was statistically significant, the absolute variation was small (0.02). Furthermore, a similar variation in MCA PI was observed between the 0 and 20 minute ultrasound assessments, during which participants breathed room air only.

	0 mins	20 mins	0 -20 mins p =	40 mins (Post O^2)	0 – 40 mins p =	60 mins	0 – 60 mins p =
UA PI	0.79 (0.52–1.24)	0.77 (0.53-1.17)	0.02	0.79 (0.52-1.24)	0.30	0.78 (0.52-1.25)	0.38
MCA PI	1.37 (0.83-1.89)	1.34 (0.82-1.90)	0.02	1.35 (0.81-1.81)	0.04	1.34 (0.81-1.81)	0.07
C/U ratio	1.79 (0.99-2.87)	1.80 (0.99-2.79)	0.77	1.78 (0.99-2.87)	0.62	1.78 (1.00-2.85)	0.56
UV Flow (ml/min)	220.5 (116.2-344.1)	221.3 (108.8-331.0)	0.69	220.2 (116.1-355.4)	0.92	222.0 (122.0-348.6)	0.64
UtA PI	0.71 (0.47-1.08)	0.73 (0.40-1.11)	0.27	0.74 (0.36-1.09)	0.25	0.72 (0.40-1.14)	0.68

Table 107. Comparison of Doppler parameters between the baseline scan (0 minutes) and each subsequent timepoint

The degree of change in the Doppler parameters between the baseline assessment, and at each additional timepoint was also evaluated (Table 106). No significant variation was identified.

	0-20mins	0-40 mins	0-60 mins	p =
UA PI	0.02 (-0.03-0.09)	0.01 (-0.08-0.08)	0.01 (-0.11-0.10)	0.69
MCA PI	0.03 (-0.08-0.12)	0.02 (-0.06-0.13)	0.03 (-0.12-0.18)	0.94
C/U ratio	-0.01 (-0.18-0.14)	0.01 (-0.13-0.20)	0.02 (-0.20-0.23)	0.78
UV Flow (ml/min)	-0.75 (-18.8-14.3)	0.32 (-20.0-31.0)	-1.46 (-20.1-34.6)	0.90
UtA PI	-0.02 (-0.19-0.07)	-0.02 (-0.18-0.13)	-0.01 (-0.24-0.22)	0.89

Table 108. Comparison of the change in Doppler parameters between baseline and each subsequent timepoint

To establish whether the fetal response to maternal Oxygen therapy was dependent on the baseline value of each Doppler parameter (measured during the 0 minute ultrasound assessment), the degree of change in each ultrasound parameter (between 0 and 40 minutes) was correlated with its baseline value (0 minutes). No significant relationships were identified (Table 107).

	Spearman correlation co-efficient (Baseline value vs. change in value)
UA PI	0.35 (95% CI -0.13-0.69, p = 0.13)
MCA PI	0.05 (95% CI -0.41-0.49, p = 0.84)
C/U ratio	0.06 (95% CI -0.40-0.50,p = 0.79)
UV Flow (ml/min)	-0.04 (95% CI -0.42-0.48, p = 0.88)
Uterine artery PI	-0.02 (95% CI -0.54-0.51, p = 0.93)

Table 109. Correlation between the degree of change in each ultrasound parameter and its baseline value

Discussion

The aim of this study was to establish whether maternal Oxygen therapy could influence flow velocity waveforms in the fetal umbilical artery, middle cerebral artery, and umbilical vein, and the maternal uterine artery. The study was powered to detect a change in the C/U ratio of 0.3 after maternal Oxygen therapy. Following Oxygen therapy, no significant change in the cerebro-umbilical ratio was identified. A significant change in the MCA PI was observed, but the absolute change in the MCA PI was small (0.02). Furthermore, a similar change was observed in both the MCA PI, and the UA PI between the 0 and 20 minute time periods. As the study was not powered to detect such small changes, these findings must be interpreted with caution. The degree of change observed, between the baseline scan and each of the three subsequent scans, were not significantly different from one another. Furthermore, the degree of change had no correlation with the initial baseline value of the Doppler parameter. These results suggest that in routine pregnancy, the resistance indices of the umbilical, middle cerebral and uterine arteries, as well umbilical venous flow, are not significantly influenced by maternal Oxygen therapy, a conclusion consistent with that of Manabe et al, who observed no change in fetal UA and MCA resistance indices following maternal Oxygen administration[(424)].

Investigation of maternal Oxygen therapy has predominantly focused on its use as a treatment for fetal growth restriction, as a consequence of the association of the chronic hypoxia of high altitude residence with low birthweight[(399)]. Whilst studies have demonstrated that increasing the concentration of maternal inspired Oxygen does result in an increased Oxygen partial pressure in the fetal circulation[(407)], and fetal growth restriction is associated with reduced Oxygen tensions[(406)], none of the randomised controlled trials evaluating maternal Oxygen therapy as a treatment for fetal growth restriction demonstrated a significant increase in birthweight[(408)].

Due to the association of hypoxia and fetal growth restriction[(431)], high altitude residence is frequently used as a model of hypoxia induced pathology[(432)]. Residence at altitude is associated with a reduced concentration of inspired Oxygen, but studies suggest that maternal adaptations, including increased ventilation and haemoglobin concentration, result in a maternal arterial Oxygen content similar to that of women at sea level[(394)]. Birthweights in ethnic groups with more than 8000 years of high altitude living are relatively protected[(433)], despite arterial Oxygen content in these women being similar to those of

more recent migrants, in whom birthweights are substantially reduced[394]. Furthermore, fetal adaptations at altitude result in increased Oxygen extraction from maternal blood, and whilst absolute Oxygen delivery is reduced at altitude, when normalised for fetal weight values are similar in low and high altitude populations[434]. These studies therefore suggest that the reduction in fetal weight associated with the relative hypoxia of high altitude residence is not secondary to hypoxia itself, but a result of maternal and fetal adaptations to hypoxia, including metabolic remodelling of the placenta itself[435]. The reduction in fetal weight may itself be a protective response designed to maintain a normal rate of Oxygen delivery. Furthermore, Krampl et observed a higher UAPI in pregnancies at altitude, but no concomitant reduction in the MCA PI[436]. The authors of this study suggested that an increased fetal haematocrit may be responsible for the absence of brain sparing despite the hypoxia of altitude. These results suggest that whilst some fetuses may show evidence of haemodynamic changes similar to those found in cases of growth restriction, these changes may not occur as a result of reduced Oxygen delivery to the fetus. Rather they may be a manifestation of changes in placental function secondary to chronic hypoperfusion/hypoxia, and as such are unlikely to be ameliorated by a short term increase in maternal inspired Oxygen concentration.

The reduction in placental function that results in fetal growth restriction and intra-partum fetal compromise is likely to affect not only gaseous exchange within the placenta, but also the transfer of other substrates critical for fetal wellbeing. As well as hypoxia, the reduced fetal growth in high altitude populations is associated with fetal hypoglycaemia and hypoinsulinaemia[432]. An increase in the consumption of Glucose by the placenta during anaerobic metabolism (in order to maintain Oxygen availability to the fetus), limiting the availability of this substrate to the fetus[432]. Even mild hypoxia can influence fetal glucose delivery, despite maintenance of adequate fetal Oxygenation[437]. If a reduction in placental function, predisposing a fetus to compromise in labour, is a result of deficiency of other substrates, short term maternal Oxygen supplementation will not remedy these deficiencies.

This study is limited by its composition of women with routine pregnancies. It is possible that maternal Oxygen therapy could influence flow velocity waveforms in cases where placental function is already reduced, such as in cases of fetal growth restriction, but have no effect in pregnancies with adequate placental function. However, even though the study population was small, it did include two cases were with a C/U ratio <10th centile (both of

which subsequently required emergency caesarean delivery for presumed fetal compromise), and no significant alteration in resistance indices was identified in these cases. Furthermore, the baseline value for each Doppler parameter had no correlation with the degree of change in that parameter following maternal Oxygen therapy.

Summary

Results from this study suggest that short term maternal Oxygen therapy, in appropriately grown term fetuses, does not influence resistance indices of the umbilical artery, middle cerebral artery, or uterine artery, nor does it affect flow rate in the umbilical vein.

Chapter 8 – Relationship between pre-labour ultrasound and development at 18-24 months

Introduction

Increasingly, an adverse intra-uterine environment is being recognised to be detrimental not only to fetal development, but also to health and development after delivery and into adult life. Fetal growth restriction is associated with an increased risk of heart disease, stroke, diabetes, and hypertension[320], an association thought to demonstrate the principle of developmental plasticity and fetal programming[438]. An adverse intra-uterine environment may also precipitate trans-generational effects, impacting the health of not only the current generation, but subsequent ones as well[439].

Fetal growth restriction and the development of a brain sparing circulation, whilst considered protective in-utero[440], are associated with an increased incidence of childhood behavioural problems[316], deficits in memory[441], reduced IQ at 5 years of age[317], and a greater requirement for special educational needs in childhood[318]. Recently, reduced performance in neurobehavioral testing has also been observed in appropriately grown fetuses with increased frontal brain perfusion[324].

The Ages and Stages Questionnaire (ASQ)[442] is a parent completed developmental screening test, that has been recommended for screening the development of low risk children[443]. Using the ASQ, parents can score their child's development in five different categories; communication, gross motor, fine motor, problem solving, and personal-social. Parent completed tools including the ASQ are reported to be an effective method of screening for developmental delay, with an average specificity and sensitivity of 86% and 85% respectively[444]. The ASQ has the added benefit of assessing development in an age-independent manner, meaning the development of children at multiple different ages may be compared.

Within the cohort of participants recruited to the early labour phase of this project, cases were identified with relatively increased cerebral perfusion (evidence by a low C/U ratio) and relatively reduced cerebral perfusion (as evidence by a high C/U ratio). This phase of the research project aimed to identify whether neurodevelopment, assessed using the

parent completed ASQ (third edition), was different between children with the lowest term C/U ratios and those with the highest term C/U ratios.

Methods

All cases recruited during the early labour phase were considered eligible for inclusion. Cases were grouped according to C/U ratio values of <10th centile, 10th-90th centile, and >90th centile. Those cases in the <10th centile and >90th centile group were selected for the study population.

For each case, the age of the child was calculated from the date of delivery. An age appropriate ASQ, request letter, and a stamp-addressed envelope (for return of the questionnaire), were then posted to each participant, requesting they complete the ASQ with their child, and return the questionnaire to the research team. In each case, participants were given a date by which the ASQ must be returned, to ensure the ASQ remained appropriate for the child's age.

On receipt of the completed questionnaires, each case was scored according to the AQA-3 age specific information summary. Overall scores, as well as those for each category, were then compared between the two C/U ratio groups. Mean scores were compared using a student's t-test/Mann Whitney test.

Results

The early labour cohort contained 604 cases, of which 58 had a C/U ratio <10th centile and 58 had a C/U ratio >90th centile. This resulted in a study population of 116. Of the 116 ASQs sent to participants, only 34.5% (40/116) were returned. Twenty one of these were cases with a C/U ratio <10th centile, and 19 were cases with a C/U ratio >90th centile. Maternal demographics between the C/U ratio centile groups were compared in the early labour phase of the project. Only gestation had significant variation between the C/U ratio centile groups, and whilst significant, the absolute difference in gestation was small (1.4 weeks), and so was not considered as a confounding factor.

Scores from the completed ASQs were analysed according to each development category, as well as the combined score.

The communication score ranged from 20 – 60, with a median of 50 (mean 46.1), and a normal distribution (D'agostino-Pearson p = 0.15). For cases with a C/U ratio < 10th centile the mean score was 48.6 (range 20 – 60), compared to 43.4 (range 20 – 60) in cases with a C/U ratio >90th centile. This difference did not reach statistical significance (p = 0.19).

The gross motor score ranged from 15 – 60, with a median of 55 (mean 51.5), and a non-normal distribution (D'agostino-Pearson p = <0.001). For cases with a C/U ratio <10th centile the mean score was 51.9 (range 20 – 60) compared to 51.1 (range 15 – 60) in cases with a C/U ratio >90th centile. This difference did not reach statistical significance.

The fine motor score ranged from 35 – 60, with a median of 55 (mean 52.9), and a normal distribution (D'agostino-Pearson p = 0.06). For cases with a C/U ratio <10th centile the mean score was 52.9 (range 35 – 60), compared to 52.9 (range 35 – 60) in cases with a C/U ratio >90th centile (p = 0.99)

The problem solving score ranged from 30 – 60, with a median of 50 (mean 50.0), and a normal distribution (D'agostino-Pearson p = 0.20). For cases with a C/U ratio <10th centile the mean score was 49.3 (range 35 – 60) compared to 50.8 (range 30 – 60) in cases with a C/U ratio >90th centile (p = 0.52).

The personal-social score ranged from 15 – 60, with a median of 50 (mean 48.0), and a non-normal distribution (D'agostino-Pearson = 0.01). For cases with a C/U ratio <10th centile the mean score was 48.3 (range 15 – 60) compared to 47.6 (range 30 – 60) in cases with a C/U ratio >90th centile (p = 0.72).

These scores resulted in a combined score ranging from 140 – 295, with a median of 252.5 (mean 248.5), and a non-normal distribution (D'agostino-Pearson p = 0.004). For cases with a C/U ratio <10th centile the mean score was 251.0 (range 140 – 285), compared to 245.8 (range 175 – 295) in cases with a C/U ratio >90th centile. This difference was not statistically significant (p = 0.52).

Scores from the ASQs were also compared between cases with a diagnosis of intra-partum fetal compromise and those without. Sixteen cases had a diagnosis of intra-partum fetal compromise. Within this group the mean total ASQ score was 245.9 (range 140 – 290), compared to 250.2 (range 200 – 295) in the 24 cases without a diagnosis of intra-partum fetal compromise. This difference did not reach statistical significance (p = 0.70).

No significant variation was found between the composite risk score groups and the total ASQ score (p = 0.69), or the composite neonatal outcome score and the total ASQ score (p = 0.50).

Discussion

Recent studies have demonstrated that cerebral redistribution in utero is associated with adverse long term neurodevelopmental outcomes[316-318, 441]. In this study we investigated the association between neurodevelopment, assessed using a parental completed questionnaire, and the C/U ratio measured at term, in an appropriately grown cohort of normal fetuses from uncomplicated pregnancies. No significant difference in neurodevelopmental outcomes was observed between fetuses with the lowest C/U ratios and those with the highest C/U ratios. Similarly, no association between a diagnosis of fetal compromise in labour and adverse neurodevelopmental outcomes was observed. Whilst no significant differences were observed, these results must be interpreted with caution as only 34.5% (40/116) of ASQs were completed and returned.

Evidence from 1st trimester levels of B-HCG and PAPP-A, and ultrasound scans performed at 35 - 37 weeks gestation, suggest that appropriately grown fetuses with a reduced C/U ratio at term do not have a sub-optimally functioning placenta throughout pregnancy, but that deterioration in placental function may occur in some cases in the late third trimester. The increased cerebral perfusion in cases with a C/U ratio <10th centile at term, by occurring later in development, may have a reduced impact on neurodevelopmental outcomes. Mula et al[324], observed an increased incidence of adverse neurodevelopmental outcomes in fetuses with increased cerebral perfusion measured using fractional moving blood volume (FMBV) between 32 and 36 weeks gestation. Interestingly, even at this gestation they did not observe an association between reduced C/U ratios and neurodevelopmental outcomes. Fractional moving blood volume measures blood flow via quantification of the returned power Doppler signal in a region of interest, and has been validated against gold standard in vivo techniques[445]. This technique is able to quantify blood flow to particular brain regions. Roza et al, found that the association between increased perfusion of the frontal lobes (assessed using the anterior cerebral artery) and subsequent 'problem behaviour' was greater than the association when perfusion was assessed using the middle cerebral artery[316]. Therefore, as evidence of increased cerebral perfusion, the relatively reduced C/U ratio observed in some cases in our study may not have the required specificity to correlate with subsequent neurodevelopmental scores. Indeed FMBV has been reported to be a more sensitive measure of cerebral distribution than conventional Doppler indices in small for gestational age fetuses[446].

The ASQ-3 assessment tool used in this study has been validated in western populations[447]. However, whilst it is suggested to be an effective tool for the detection of severe developmental delay, its accuracy in mild cases appears more limited[448]. Given that in our cohort the infants studied were from a 'normal' population, any deficits in neurodevelopmental outcomes are likely to be subtle. The ASQ may lack the sensitivity to detect such subtle changes.

Chapter 9 – Conclusions and further work

This aim of this thesis was to investigate the relationship between ultrasound markers of fetal wellbeing and intra-partum and neonatal outcomes. Results from the early labour study (Chapter 3) demonstrated that ultrasound assessment in early labour could identify babies at high and low risk of a subsequent diagnosis of intra-partum fetal compromise, and the need for emergency delivery. The UA PI, MCA PI, C/U ratio, and UV flow rate were found to be predictive of subsequent intra-partum fetal compromise The C/U ratio was found to be the most predictive marker when used in isolation. The performance of these Doppler parameters when used as a diagnostic test is detailed in tables 108, 109. For this comparison a positive test was considered a UA PI >90th centile, or an MCA PI, C/U ratio, or UV flow rate <10th centile, or a composite risk score of 7-8.

To predict emergency caesarean delivery for presumed fetal compromise (Table 108).

	Specificity	Sensitivity	PPV	Positive Liklihood ratio
UA PI	90.8% (88.0% - 93.1%)	14.5% (7.5% - 25.5%)	17.0% (8.9% - 29.4%)	1.58 (95% CI 0.84 – 2.98)
MCA PI	92.5% (89.9% - 94.5%)	20.3% (11.9% - 32.0%)	25.9% (15.4% - 39.9%)	2.71 (95% CI 1.56 – 4.73)
C/U ratio	93.1% (90.5% - 95.0%)	30.4% (20.2% - 42.8%)	36.2% (24.3% - 50.0%)	4.40 (95% CI 2.74 – 7.06)
UV flow	90.6% (87.7% - 92.9%)	14.5% (7.5% - 25.5%)	16.7% (8.7% - 29.0%)	1.54 (95% CI 0.82 – 2.90)
Composite risk score	98.7% (97.2% – 99.4%)	11.6% (5.5% – 22.1%)	53.3% (27.4% – 77.7%)	8.82 (95% CI 3.30 – 23.59)

Table 110. Prediction of caesarean delivery for presumed fetal compromise

To predict a diagnosis of fetal compromise during labour (Table 109).

	Specificity	Sensitivity	PPV	Positive Liklihood ratio
UA PI	90.8% (87.6% - 93.3%)	11.2% (7.1% - 16.9%)	33.9% (22.4% - 47.5%)	1.22 (0.73 – 2.03)
MCA PI	92.7% (89.7% - 94.9%)	12.9% (8.5% - 18.9%)	42.6% (29.5% - 56.7%)	1.76 (95% CI 1.06 – 2.93)
C/U ratio	94.1% (91.3% - 96.1%)	18.4% (13.2% - 25.1%)	56.9% (43.3% - 69.7%)	3.13 (1.92 – 5.11)
UV flow	91.7% (88.6% - 94.1%)	14.0% (9.4% - 20.1%)	41.7% (29.3% - 55.1%)	1.69 (95% CI 1.04 – 2.73)
Composite risk score	99.3% (97.8% – 99.8%)	6.7% (3.7% - 11.7%)	80.0% (51.4% - 94.7%)	9.45 (95% CI 2.70 – 33.09)

Table 111. Prediction of a diagnosis of fetal compromise during labour

The negative predictive value, for caesarean section for presumed fetal compromise, of ultrasound parameters suggestive of good placental function can also be assessed. For this analysis a negative test was considered to be a UA PI <10th centile, or an MCA PI, C/U ratio, or UV flow >90th centile, or a composite risk score of 0-2 (Table 110).

	Specificity	Sensitivity	NPV	Negative Likelihood ratio
UA PI	8.6% (6.4% - 11.4%)	94.2% (85.1% - 98.1%)	92.0% (79.9% - 97.4%)	0.67 (95% CI 0.25 – 1.81)
MCA PI	9.5% (7.2% - 12.4%)	95.7% (87.0% - 98.9%)	94.4% (83.7% - 98.6%)	0.46 (95% CI 0.15 – 1.43)
C/U ratio	10.7% (8.2% - 13.7%)	98.6% (91.1% - 99.9%)	98.3% (89.5% - 99.9%)	0.14 (95% CI 0.02 – 0.98)
UV flow	10.3% (7.9% - 13.3%)	92.8% (83.2% - 97.3%)	91.7% (80.9% - 96.9%)	0.70 (95% CI 0.29 – 1.69)
Composite risk score	9.8% (7.4% - 12.7%)	97.1% (90.0% - 99.5%)	96.3% (86.2% - 99.4%)	0.30 (95% CI 0.07 – 1.20)

Table 112. Negative predictive value and negative likelihood ratio of reassuring ultrasound parameters

Of all the Doppler parameters, a low C/U ratio (<10th centile) had the best positive predictive value for caesarean delivery (36.2%) and for fetal compromise during labour (56.9%), as well as the highest positive likelihood ratios (4.40 and 3.13 respectively. A high C/U ratio (>90th centile) also had the best negative predictive value for caesarean delivery (98.3%) and the lowest negative likelihood ratio (0.14). Results from the early labour phase of this project

suggest that babies with the lowest C/U ratios are 21 times more likely to require emergency caesarean delivery for presumed fetal compromise than those with the highest C/U ratios. Whilst the 95% confidence intervals for these measures do overlap with those of the UA PI and MCA PI, it should be noted that the study was not powered to demonstrate statistically significant differences in these indices. Furthermore, regression analysis does suggest that the C/U ratio is a better predictor of caesarean delivery for presumed fetal compromise than either of its constituent components used alone.

The value of the C/U ratio as a marker of fetal compromise has been investigated in other published reports. Devine et al evaluated a number of techniques used to monitor postdates pregnancy including the C/U ratio, biophysical profile and AFI. They found a C/U ratio of <1.05 to be the most accurate predictor of adverse outcome[(449)]. Siristatidis et al measured the C/U ratio of fetuses during abnormal CTG recordings, with caesarean section being indicated if the C/U ratio was <1 for more than 2 minutes. They found the use of the C/U ratio led to a significant reduction in rates of caesarean section, with no adverse effect on neonatal outcome reported[(450)]. Data from this study supports these findings, but also suggests that the C/U ratio can have a predictive role, identifying prior to active labour fetuses at high and low risk of subsequently developing signs of fetal compromise. In contrast, a recent report published by D'Antonio et al concluded the cerebro-umbilical ratio was not predictive of adverse outcome in a population of otherwise normal post term pregnancies[(451)]. In the D'Antonio study the incidence of 'adverse pregnancy outcome' was compared between fetuses above and below a C/U ratio cut off value. "Adverse pregnancy outcome' was defined as operative delivery for presumed fetal compromise (based on ST segment analyses), but also umbilical artery pH<7.15 and a base excess < -11mmol/L. As a result, the population of cases defined as having an adverse pregnancy outcome, is likely to have included several cases where acidosis at delivery was not associated with signs of compromise during labour. Neonatal outcomes from the early labour cohort in this study, demonstrate that fetuses born by SVD had the second highest rate of acidosis at delivery. It is therefore possible that the 'adverse pregnancy outcome' group of the D'Antonio study is likely to have included several cases born by SVD. In fact, of the 58 cases the authors reported as having an 'adverse outcome' only 22 were delivered by emergency caesarean delivery.

Whilst the C/U ratio, used alone as a predictor of fetal compromise, may not have a positive likelihood ratio sufficient to guide mode decisions regarding mode of delivery, the good

negative likelihood ratio offered by a high C/U ratio does have potential to guide place of delivery decisions in some circumstances. Knowledge that the likelihood of intra-partum fetal compromise was extremely low, may encourage women to consider birth away from an obstetric setting, which evidence suggests may be associated with reduced intervention[452].

Whilst significant differences in fetal haemodynamics were observed between the different mode of delivery groups, no significant variation was found in uterine artery PI. The absence of an association between uterine artery PI and cases of intra-partum fetal compromise is suggestive that the reduced placental function in these babies (evidenced by reduced C/U ratios) is not the result of early abnormal placentation. Abnormal placentation is associated with a raised uterine artery PI[453], secondary to the persistence of a high resistance placental circulation[249]. This process is implicated in fetal growth restriction, with sub optimal trophoblastic invasion and a failure of the conversion of spiral arteries to a low resistance form during placental development the likely cause[454].

Both ultrasound parameters at 35-37 weeks gestation (Chapter 4) and 1st trimester B-HCG/PAPP-A values (Chapter 5) showed no correlation with subsequent intra-partum fetal compromise. These results are also suggestive that a reduction in placental function in the late third trimester, rather than abnormal placentation per se, may predispose some appropriately grown fetuses to intra-partum compromise. Alongside this concept of 'placental ageing', there is also potential for the fetal demands placed on the placenta to change between 36 weeks gestation and term. Umbilical venous flow, which may be considered representative of fetal oxygen and nutrient supply, gradually increases with advancing gestation[233]. This increased perfusion places increasing demands on both passive and active transport of nutrients, as well as gaseous transfer across the maternal-fetal interface within the placenta. The placenta responds to these increasing demands with a continuous increase in size throughout pregnancy[455]. However, for a given birthweight, placental weights are lower in SGA fetuses than their AGA counterparts[60], and reduced placental weight has also been associated with intra-partum fetal compromise[61]. A failure to maintain adequate placental growth to satisfy increasing fetal nutritional demands in late gestation may therefore have an adverse influence on the feto-placental relationship, predisposing the fetus to compromise in labour.

Neonatal outcomes

Early labour ultrasound assessment was not found to be predictive of the neonatal condition at birth, assessed using Apgar scores, umbilical artery pH and base excess, and the requirement for neonatal unit admission. Interestingly, babies born by instrumental delivery for presumed fetal compromise had the poorest condition at birth, whilst those delivered by caesarean for presumed fetal compromise had the second best composite neonatal outcome score of all mode of delivery groups. These results suggest that the condition at birth may be influenced not only by fetal wellbeing throughout labour, but also by other factors including the mode of delivery itself, and periods of intra-uterine fetal resuscitation. For example, following a decision to deliver a fetus by emergency caesarean for presumed fetal compromise, a mother may be treated with high concentration oxygen therapy, placed in a left lateral position, and have any oxytocin augmentation stopped. These measures may allow for improvement in the condition of the fetus. In contrast, the decision to deliver a fetus by instrumental delivery may be followed by a prolonged and sometimes difficult delivery, resulting in a potential deterioration in the neonatal outcome variables. Bloom et al[456] compared neonatal outcomes in infants delivered by emergency caesarean for fetal compromise both within 30 minutes of the decision to deliver, and after 30 minutes. Neonatal outcomes were worse in the group of infants delivered fastest. The authors suggest this relates to the greater urgency with which the more clinically compromised infants were delivered. However, it may also relate to the shorter period of "fetal resuscitation" prior to delivery. This conclusion is supported by the author's observation that of the infants delivered greater than 30 minutes following a decision to deliver, 95% did not experience a single measure of neonatal compromise.

The potential for neonatal outcome variables to be influenced in this way casts doubt on the appropriateness of their frequent use as measures of intra-partum compromise. Whilst an Apgar score <7 at five minutes is associated with an increased relative risk of subsequent cerebral palsy, epilepsy, and cognitive impairment, the absolute risk of adverse outcomes in these cases is still small[457]. Evidence from magnetic resonance imaging (MRI) studies suggest moderate or severe brain lesions are predominantly associated with an Apgar score of <3 at one minute, and that even within this group, 28% of cases had normal imaging or only minor white matter changes[458]. As demonstrated in the early labour cohort (incidence of Apgar <3 at one minute 0.8%, Apgar <7 at five minutes 1.0%), such low Apgar scores occur very rarely within a normal population, meaning very large study populations are required to

make statistically valid conclusions. As a consequence, many studies (including the current project) evaluating intra-partum monitoring techniques as predictors of intra-partum compromise have chosen to use the incidence of a less abnormal Apgar score as a marker of neonatal outcome. However, in the absence of a correlation between these Apgar scores and subsequent long term effects, it is impossible to conclude whether these scores are associated with true intra-partum fetal compromise or a consequence of the delivery process itself.

Low umbilical artery pH at delivery is associated with subsequent neonatal mortality and long term morbidity. However, there is a strong dose-response relationship with the association between a pH of <7.00 and adverse outcomes far stronger than that of a pH <7.20 but >7.00[459]. Whilst neonatal encephalopathy and subsequent cerebral palsy are rare outcomes amongst a normal population, a pH of <7.20 at delivery occurs relatively frequency, even amongst cases with no evidence of compromise during labour (25% in the instrumental for prolonged 2nd stage group). This suggests reductions in umbilical artery pH may be a consequence of the mode of delivery itself, and not necessarily indicative of a compromised fetus.

The composite risk score

In Chapter 6, ultrasound markers from the early labour cohort were combined to create a composite risk score. Using this scoring system, the excellent negative predictive value (98.3%) conferred by a high C/U ratio is largely maintained, but a high composite risk score offers a better positive predictive value than a low C/U ratio used in isolation (53.3% vs. 36.2%), and a better positive likelihood ratio (8.8 vs. 4.4). Whilst these results must be interpreted with caution, as the 95% confidence intervals for these indices did overlap with those of the individual ultrasound parameters, the study was not powered to demonstrate these differences. A larger prospective study is required to confirm whether the composite risk score offers additional benefit, beyond that of its constituent parameters.

The composite risk score identified a cohort of women, representing 9% of the study population (54/604), in whom the likelihood of caesarean delivery for fetal compromise was extremely low (3.7%). Recently, analysis of almost 14 million births in the United States found significantly increased risk of an Apgar score of 0 at five minutes, neonatal seizures, and significant neurological dysfunction in births that took place outside of a hospital setting[(460)]. Interestingly, births outside of a hospital setting were composed of a greater proportion of multiparous women, pregnancies that should have a reduced incidence of complications. The Birthplace in England and Wales study also demonstrated increased risk of adverse neonatal outcomes in nulliparous women delivering outside of a hospital setting, but also reduced intervention rates[(452)]. The composite risk score described here could be used as a screening tool to guide decisions regarding birthplace setting, potentially reducing the incidence of adverse outcomes in non-hospital settings. This technique could be easily transferred to clinical practice, and used in this way would not result in the requirement to image a large number of babies at term, given that currently only a small percentage of women choose to have a homebirth[(461)]. It is likely that prior knowledge regarding the likelihood of the fetus becoming distressed in labour would influence maternal decision making, potentially encouraging more women to consider birth outside an obstetric unit in low risk cases, whilst ensuring high risk cases were delivered in an appropriate environment.

Maternal Oxygen therapy

In chapter 7, the use of maternal Oxygen therapy as a potential therapeutic measure was investigated. Maternal Oxygen therapy, at the dosage used in this study, did not lead to any significant improvement in the measured Doppler indices. The study population was predominantly composed of babies with 'normal' ultrasound parameters, in which an increased risk of intra-partum fetal compromise was not anticipated. Further investigation is required to evaluate maternal Oxygen therapy in an at risk population (i.e. babies with low C/U ratios/high composite risk scores).

Why do increased operative delivery rates matter?

Globally, caesarean section rates have risen significantly over the last 30 years, with considerable international variation from 0.4% to 40%[462]. The introduction of continuous fetal monitoring has been held partly responsible for this rise[9]. Whilst debate surrounds the optimal caesarean section rate,[463, 464], a frequently quoted figure of 15%, reached after evaluating caesarean section rates in countries with the lowest rates of maternal and neonatal mortality, was suggested by the World Health Organisation in 1985. Evidence also suggests that whilst not resulting in improved outcomes, increased caesarean section rates may result in increased maternal morbidity, even after adjustment for risk factors[465]. It is estimated that in Latin America, home to some of the world's highest caesarean section rates, 1.5 million unnecessary caesarean sections are performed each year, contributing to 100 maternal deaths and 40000 cases of neonatal respiratory morbidity[466].

Caesarean section is now an extremely safe surgical procedure, but it does have recognised complications. Liu et al compared spontaneous vaginal delivery with elective caesarean section and found a three times higher rate of severe maternal morbidity in the elective caesarean group. Within this study, the caesarean section group had an increased risk of cardiac arrest (OR 5.1), venous thrombo-embolism (OR 2.1), infection (OR 3.1), and haemorrhage requiring hysterectomy (OR 2.1)[467]. Infants born by caesarean section are known to have increased rates of respiratory complications when compared to those born by vaginal delivery[468]. In less developed countries, where the risks associated with caesarean delivery are greater[469], accurate identification of intra-partum fetal compromise and the prevention of unnecessary caesarean section, is even more paramount.

In the UK, where the current caesarean section rate is around 24%[470], a 1% rise is estimated to cost the National Health Service an additional £5million each year[471]. Reducing unnecessary caesarean sections may therefore result in both a reduction in morbidity and mortality rates as well as financial expenditure. With the NHS facing some of the most stringent financial restrictions in its history, safely reducing caesarean section rates, would result in significant benefit to the NHS.

As a result of these potential benefits, obstetric units are now under increasing medical, political, and economic pressure to reduce rates of caesarean section, and increase rates of home births and those in midwifery led units. Experience from the recent Birthplace study[452] suggests planned delivery outside of an Obstetric unit is associated with a reduced incidence of intervention and a higher percentage of "normal births". When considering multiparous women alone, no difference in adverse perinatal outcome was observed. However, the babies of nulliparous women who planned a home delivery were at increased risk of adverse outcomes. Furthermore, transfer rates from all non-obstetric units were noted to be high, around 30% for nulliparous women and 6-8% for multiparous women. This data suggests that whilst birth outside of an obstetric unit may be beneficial for some low risk pregnancies, with reduced intervention and no increased risk of complications, improved selection of women suitable for delivery outside of an obstetric unit is required. Better risk stratification of pregnancies prior to labour, would facilitate more informed decisions regarding mode and place of delivery, potentially reducing unnecessary interventions, and improving both maternal and neonatal outcomes.

Further work

Through this research study, ultrasound parameters have been identified that are associated with both an increased and reduced incidence of fetal compromise during labour. The observation that flow velocity waveforms of the umbilical artery, middle cerebral artery, and umbilical vein, are indicative of placental function, even in the appropriately grown fetus, raises several further research questions.

Can the predictive value of these markers be improved?

Whilst an increased UA PI, reduced MCA PI, reduced C/U ratio, and reduced UV flow rate when measured in early labour were all associated with an increased incidence of subsequent caesarean delivery for presumed fetal compromise, the positive predictive value for all these markers used in isolation was low. Even when combined as a composite risk score, the majority of caesarean deliveries for presumed fetal compromise still occurred in cases outside the highest risk score group. Results from both the 36 week cohort and from analysis of 1st trimester B-HCG and PAPP-A levels suggest that normal pregnancies affected by fetal compromise in labour are likely to have had an adequately functioning placenta for the majority of the pregnancy, and that it is the change in placental function toward the end of pregnancy that may manifest as intra-partum fetal compromise. It is therefore possible that longitudinal assessment of UA PI, MCA PI, the C/U ratio, and UV flow, in a cohort of normal pregnancies, may identify cases in which there is a significant deterioration in these markers in the last few weeks of pregnancy. Potentially, the degree of deterioration may be a more accurate predictor of subsequent intra-partum fetal compromise than the absolute value of these parameters when measured at term. This research question could be answered by a prospective observational study, with a cohort of women with low risk pregnancies recruited at 36 weeks. Ultrasound assessments could be performed weekly until delivery, and intra-partum and neonatal outcomes correlated both with the absolute values of each ultrasound parameter, but also with the gradient of change observed between the weekly ultrasound assessments.

Multiple biochemical markers have been suggested to be informative of placental function[(298)]. Assessment of first trimester B-HCG and PAPP-A levels in this study did not demonstrate a relationship with subsequent intra-partum fetal compromise, or with ultrasound parameters measured at term. However, assessment of these markers, as well

as others, in the third trimester or prior to labour, may be more informative of placental function at that stage of pregnancy. Combining biochemical markers of placental function with ultrasound parameters may result in a more predictive test. Furthermore, the use of other techniques such as proteomics may offer further insight into fetal wellbeing. A proteomic profile consistent with intra-amniotic inflammation has already been established[472] and been demonstrated to correlate with non-reassuring features on fetal heart rate monitoring in a pre-term population[473]. Alterations in the proteomic signature of umbilical cord blood has also been reported in cases of fetal growth restriction[474], and markers of pre-eclampsia identified in maternal urine[475]. Application of this technique to intra-partum fetal compromise may allow identification of new predictive or diagnostic markers.

Is there potential for clinical application of this technique?

The observation that fetal haemodynamics provide information regarding placental function in the appropriately grown fetus, as well as in cases of small for gestational age, may enable better monitoring of routine pregnancy. Sadly, a significant proportion of stillbirths are unexplained, occurring in routine pregnancies with no identifiable risk factors[476]. The proportion of stillbirths classified as unexplained also increases with advancing gestation[476]. It is possible that at least some of these stillbirths occur following a deterioration of placental function, in an already adequately grown fetus. Such deterioration may be evidenced by changes in fetal haemodynamics.

Stillbirth is more common in post term pregnancy[477]. As a result induction of labour after 41 weeks gestation is routinely offered to women at many Obstetric units. For older mothers, due to the associated increased incidence of post-term stillbirth[478], induction may be offered at earlier gestations. Whilst this policy is designed to reduce the incidence of still birth, it is criticised by many vocal advocates of normal birth who insist it precipitates a 'cascade of intervention'[479]. Currently, no technique exists to facilitate an individualised approach to the management of postdates pregnancy. Potentially, assessment of fetal haemodynamics at 41 weeks gestation (or earlier in older mothers) may enable identification of pregnancies where placental function is relatively reduced which would benefit from induction of labour, whilst also identifying those pregnancies with adequate placental function where an expectant approach to management is appropriate. Such a technique would result in a significant reduction in the number of women requiring

induction of labour for post term pregnancy, and may result in both an increased incidence of normal birth, and a reduced incidence of stillbirth.

Combining pre-labour assessment with current intra-partum monitoring regimes is another potential clinical application of this technique. Continuous fetal heart rate monitoring is hampered by its inherent poor specificity[94]. As a result the use of continuous monitoring in routine pregnancy is not advised[99]. This policy is designed to limit the impact a test with a high false positive rate has on this low risk cohort. However, women undergoing induction of labour, where antenatal complications are limited to post-dates pregnancy, are not afforded this protection and routinely have continuous fetal heart rate monitoring during labour. As a result there is potential for greater intervention in these cases following the occurrence of false positive fetal heart rate patterns. Whilst in induced labour it is paramount to observe the frequency of stimulated uterine contractions, fetal heart rate monitoring may not be a necessity in all cases. Assessment of fetal haemodynamics prior to induction of labour could be used to allocate women to continuous or intermittent intra-partum fetal monitoring. This technique could potentially reduce intervention rates in these cases by limiting the exposure of all inductions to the poor specificity of continuous fetal heart rate monitoring.

Recent publications

Recently, a number of studies have been published examining the association of a low C/U ratio with adverse outcomes. These studies report retrospective data, that was not collected with the subsequent analysis in mind. Nevertheless, they add to knowledge and warrant consideration.

In 2014, Khalil et al reported a retrospective cohort study, examining data collected over a 14 year period at a tertiary referral hospital in the UK. All included cases had an ultrasound assessment performed within 2 weeks of delivery. The authors report that the C/U ratio (adjusted for gestation and presented as multiples of the median) was independently associated with the risk of operative delivery for presumed fetal compromise (odds ratio 0.67, 95% CI 0.52 – 0.87, p=0.003), supporting the conclusions of our study. In their large retrospective analysis, the authors were also able to demonstrate the C/U ratio as an independent predictor of neonatal unit admission (odds ratio 0.55, 95% CI 0.33 – 0.92, p=0.021)[480].

A further large cohort study was published in April 2015, in which Bakalis et al report a retrospective analysis of data collected at three UK hospitals between May 2011 and August 2014[481]. The authors examined data from ultrasound scans performed between 30 and 34 weeks gestation and the association of the C/U ratio measured at this gestation with a number of subsequent adverse outcomes. The authors report that the C/U ratio was a poor predictor of adverse outcome, but did note that the performance was improved in cases scanned within 2 weeks of delivery. This retrospective analysis can therefore not be compared to the prospective data reported in our study. There is clearly significant potential for placental function to change between an ultrasound assessment at 30-34 weeks gestation and subsequent delivery at term. While the number of patients in this retrospective analysis is large (30,780), only 27 cases underwent Caesarean delivery for presumed fetal compromise within two weeks of the ultrasound assessment, less than half the number reported in our prospective study. Furthermore, these cases would by definition have been delivered premature (<37 weeks gestation) and the results of this study are therefore likely to be significantly confounded.

A further study published by the same research group evaluated the performance of the C/U ratio measured at 35 – 38 weeks gestation , again concluding the C/U ratio was a poor predictor of adverse outcome[482]. However, the authors reported the C/U ratio was more predictive of caesarean delivery for presumed fetal compromise when the assessment was performed within two weeks of delivery. Despite a large number of included cases (6038), only 59 caesarean deliveries for presumed fetal compromise occurred within two weeks of the ultrasound assessment. Importantly, in each of these retrospective studies, staff managing the labour would not have been blinded to the ultrasound assessment. Furthermore, the latter two studies were conducted across 3 different sites, with potential for significant disparity in the threshold required for a diagnosis of intra-partum fetal compromise. Despite their limitations, these studies do suggest that when measured distant from labour, the performance of the C/U ratio or other parameters to predict intra-partum compromise are likely to be diminished. Neither study assessed the predictive performance of a high C/U, which in our study proved to have a close to 100% negative predictive value for caesarean delivery for presumed fetal compromise and negative likelihood ratio of 0.14 (95% CI 0.02 – 0.98).

Conclusion

Ultrasound assessment in early labour can identify babies at high and low risk of subsequent intra-partum compromise. The C/U ratio is the most predictive individual parameter, but combining assessment of the UA PI, MCA PI, C/U ratio and UV flow as a composite risk score may be more predictive than any parameter used in isolation. Whilst additional prospective studies are required to further evaluate the clinical application of this technique, potential applications include risk stratification of pregnancies prior to labour, to enable more informed decisions regarding place of delivery, as well as enabling a more targeted approach to intra-partum monitoring.

The observation that fetal Dopplers are indicative of placental function, even amongst appropriately grown fetuses, means they may be further utilised in fetal assessment. For example, this technique has potential to be used in the management of post-dates pregnancy. Babies with reduced placental function at risk of stillbirth, in whom induction of labour would be beneficial, could be distinguished from those with good placental function where expectant management may be more appropriate. Further investigation of this technique using randomised controlled trials is essential before any clinical application.

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Please let us know if you have questions.

Sincerely,
Katrina Ashworth

Appendices

Appendix A

Information sheet for volunteers

You will be given a copy of this information sheet

Study title

Does UA/MCA resistance ratio at the start of labour predict obstetric/neonatal outcome?

Invitation to take part

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

Blood flow to a baby's organs is known to change during periods of stress. These changes are particularly marked in small babies. Some babies become stressed during labour. We want to determine if ultrasound assessment of blood flow in the umbilical artery and brain at the start of labour are predictive of obstetric and neonatal complications.

If we have a way of identifying babies likely to become distressed in labour, it would help us better manage these pregnancies and hopefully improve the outcome for these babies.

Why have I been chosen?

You have been chosen because you are in early labour or are likely to go into labour within 48 hours.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form. If you decide not to, you will continue to receive standard management and your decision will in no way affect the care you receive.

What will happen to me if I take part?

If you decide to take part you will be given this information sheet to keep and we will ask you to sign a consent form. We will then perform a short ultrasound scan of your baby (lasting around 15 minutes). We will measure the size of your baby, blood flow in various vessels and the amount of amniotic fluid surrounding the baby. Once this is done your labour will be managed in the usual manner. The information obtained from the ultrasound scan will not be available to either the doctors or midwives looking after you. We would also take a drop of blood from you in early labour and again within 24 hours of delivery.

We would also take a drop of blood from your baby's heel (heel prick test) within the first 24 hours after birth. This method of taking blood from a baby is very safe and is used routinely. You may be contacted following delivery regarding the development of the baby.

All babies born to mothers recruited in this study will have heel prick samples performed at 24 hours of life to obtain dried blood spots for later analysis.

Are there any side effects of obstetric ultrasound?

There are no reported serious side effects with antenatal ultrasound.

What are the possible benefits of taking part?

There are no immediate benefits to you from taking part. However, the information gathered from this study may be of benefit for other pregnancies.

Will my taking part in this study be kept confidential?

The information obtained from your study is covered by the Data Protection Act. The computerised information is protected by a software and hardware barrier and the records are handled in the same way as hospital records. We also seek permission to include clinical details about your pregnancy in the study, for instance your gestation and medical history.

Who is organising the research?

The Centre for Fetal Care at Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare Trust is organising this research.

Who has reviewed this study?

This study has been reviewed by the principal investigator and his collaborators. The London Research Ethics Committee has approved this research.

What if something goes wrong?

In the unlikely event of you suffering any adverse effects as a consequence of your participation in the study you will be compensated through the Imperial College London's "No fault Compensation scheme."

What will happen to the results of the research study?

The results are usually published in the medical literature. **No** patient's names or identifiable data will be included.

Who is organising and funding the research?

The research is organised and funded by Imperial College London.

Contact for Further Information

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Appendix B

Patient Consent form for inclusion in UA/MCA ratio study **Tel____**

I …….. have read the attached information sheet regarding the study

“Does UA/MCA resistance ratio at the start of labour predict obstetric/neonatal outcome?”

And I would like to participate.

Signed

Patient_____ Date_____

Person taking Consent_____ Date_____

Appendix C

Low risk pregnancy defined as:-
Singleton
Term (37 – 42 weeks gestation)
No evidence of placental dysfunction – SGA/PET/PIH
No evidence of fetal compromise

Appendix D
Data Collection proforma

UA/MCA resistance ratio study

Maternal Demographics

Hospital Number_____ DOB_____
Age_____
Ethnicity_____ BMI_____

Smoker YES/NO Partner Yes/No Weight in Labour_____

Parity_____ Previous SB/IUGR_____

Booking Bp____ Raised Bp in pregnancy___

Pre existing medical condition_____

Date of booking Scan_____

Labour Details

Spontaneous labour YES/NO

Induction YES/NO If Yes Indication_____

Gestation at IOL/onset of labour_____

Membranes: Intact/Ruptured At ROM Liquor: CLEAR/MECI/MECII/MECIII

Cervical Dilatation at time of USS_____

CTG pre labour YES/NO If Yes describe_____

Length of Labour 1st stage_____ Time from ROM to delivery_____
2nd stage_____
3rd stage_____
Total_____

Mode of Delivery: SVD/Forceps/Vacuum/EmLSCS

If instrumental/Em LSCS why _____

Intra-partum Hypertension YES/NO Meconium during labour YES/NO

Intra-partum Pyrexia YES/NO Intrapartum Abx YES/NO

Associated Fetal Tachycardia YES/NO If Yes BR Rate_____

CTG abnormalities YES/NO

If yes describe_____

FBS YES/NO Number_____ Results_____

Intra-partum haemorrhage YES/NO

Intrapartum USS details

Date of Scan_____

Growth Fetal Position _____

- BPD_____
- HC_____
- AC_____
- FL_____
- EFW_____

		1	2	3
UA	**PI**			
	RI			
	SD ratio			
	Vmax			
	Tamax			
	EDF			
	Vessel Diameter			

		1	2	3
MCA	**PI**			
	RI			
	SD ratio			
	Vmax			
	Vessel Diameter			

		1	2	3
Uterine Artery	**PI**			
	RI			
	SD ratio			
	Vmax			
	Vessel Diameter			

		1	2	3
UV	**Area**			
	Vmax			
	PI			
	Vessel Diameter			

MCA/UA PI ratio : _____ Ductus_____

AFI_____ Deepest Vertical Pool_____

Nuchal cord YES/NO

Labour Outcome

Date of Delivery_____

Gestation at delivery_____ Birth Weight_____
Sex M / F

Apgars_____ Cord Gases_____

Placental Weight_____ BE_____

Admission to NNU YES/NO Lactate_____ _____

- Reason for admission_____ PO2_____ _____
- Length of stay_____ PCO2_____ _____
  Gluc_____ _____
  Na _____ _____
  Cl _____ _____
- Ventilation_____ Ca _____ _____
- Sepsis_____
- NEC
- Cranial USS/MRI_____
- Other complications_____
- Discharge summary YES/NO

Appendix E

Influence of maternal Oxygen therapy on feto-placental blood flow

Patient Information Leaflet

Researchers:

Professor Sailesh Kumar and Dr Tomas Prior
Mater Research Institute/University of Queensland

Invitation to take part

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information. Ask us if there is anything that is not clear or if you would like more information.

You will be given a copy of this information sheet to keep should you agree to participate.

1. **What is the purpose of this study?**

Blood flow to a baby's organs is known to change during periods of stress, such as during labour. These changes are particularly marked in small babies but research has recently demonstrated that normally grown babies may also show these changes, and if present these babies can be at increased risk of developing problems during labour and needing emergency delivery.

If these babies can be identified, we may be able to treat these babies, and improve the likelihood of them tolerating the stress of labour and delivery.

Research studies have suggested that small babies with changes in blood flow might be helped by giving Oxygen therapy to their mother. We want to find out if giving maternal oxygen therapy can improve the blood flow to the baby, and reduce the likelihood of the baby becoming distressed in labour and needing emergency delivery.

2. **Why have I been chosen?**

You have been chosen because you are in early labour or are likely to go into labour within 72 hours.

3. **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form. If you decide not to, you will continue to receive standard management and your decision will in not affect the care you receive in any way.

4. What will happen to me if I take part?

This research study is a self-controlled case series. Sometimes because we do not know which way of treating patients is best, we need to make comparisons. In this trial, we will be making a comparison between a treatment, Oxygen, and no treatment. The way this will happen is explained below.

If you decide to take part you will be given this information sheet to keep and we will ask you to sign a consent form. We will then perform a short ultrasound scan of your baby (lasting around 15 minutes). We will measure the size of your baby, blood flow in various vessels and the amount of amniotic fluid surrounding the baby. After 15 minutes we will repeat the measurements of blood flow. Following this you will be asked to breathe 60% Oxygen for 20 minutes. After 20 minutes, we will then perform another, shorter ultrasound scan to measure the blood flow again, with these measurements repeated after a further 20, and 40 minutes.

Once this is done your labour will be managed in the usual manner. The information obtained from the ultrasound scan will not be available to either the doctors or midwives looking after you, this is to minimise bias.

5. What is the medication being tested?

The medication being tested is inhaled 60% medical oxygen. This is the same oxygen that is already used routinely in many pregnancies. Normal air contains only around 21% oxygen.

6. Are there any side effects of maternal oxygen therapy?

Oxygen is already used routinely during labour if it is felt that the baby is in distress. Some women with respiratory and cardiac problems will also receive oxygen therapy during labour. Various studies have been performed on the use of oxygen therapy in labour and have not shown any adverse effects.

7. Are there any side effects of obstetric ultrasound?

There are no reported serious side effects with antenatal ultrasound.

8. **What are the possible benefits of taking part?**

There are no immediate benefits to you from taking part. However, the information gathered from this study may be of benefit for other pregnancies.

9. What are the possible disadvantages of taking part?

If you decide to take part in this study, we will need you to stay in the hospital for 90 minutes following the initial ultrasound scan. There are no other anticipated disadvantages to taking part.

10. **Will my taking part in this study be kept confidential?**

The information obtained from your involvement in this study is covered by the Data Protection Act. The computerised information is protected by a software and hardware barrier and the records are handled in the same way as hospital records. We also seek permission to include clinical details about your pregnancy in the study, for instance your gestation and medical history.

11. Who is organising and funding the research?

The Mater Research Institute/University of Queensland is organising this research study, it is funded by a charity called The Moonbeam Trust.

12. Who has reviewed this study?

This study has been reviewed by the Chief investigator and his collaborators. The Research Ethics Committee has reviewed and approved this research.

13. **What if something goes wrong?**

If you feel you have been harmed by taking part in this research project you should discuss this with the clinic team. They will advise you on the likelihood of your participation in the trial causing the problem. The Sponsor, Mater Research Institute, has made arrangements to cover no-fault compensation for harm caused by the trial that could not have been anticipated, and holds insurance policies which apply to this study.

This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for legal action.

If you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator:

- Professor Sailesh Kumar, tel +617 31632564

The normal Mater Health complaint mechanisms are also available to you.

14. **What will happen to the results of the research study?**

The results from this study will be stored in a re-identifiable format for up to 10 years following completion of the research. This is to enable further analysis of the results should it be required in light of future research. The data will be stored as an encrypted computer file in a locked office within the Mater Research Institute. Only authorised researchers will be able to access the data.

The results of this study will be published in the medical literature. **No** patient's names or identifiable data will be included.

Contact for Further Information

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Thank you for reading this leaflet.

Appendix F

Maternal Oxygen therapy to reduce the risk of intra-partum fetal compromise

Informed consent form

Chief Investigator: Dr Sailesh Kumar
Principle investigators: Dr Tomas Prior, Prof. Phillip Bennett

Please enter initials

1. I confirm that I have read and understand the study information sheet dated ……..version…….and have had the opportunity to ask questions which have been fully answered. ☐

2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, and without affecting my medical care or legal rights. ☐

3. I understand that sections of my notes may be looked at by responsible individuals from Mater Research Institute/University of Queensland, or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to access my records as is relevant to this research study. ☐

4. The compensation arrangements have been discussed with me. ☐

5. I agree to take part in this study. ☐

_____	_____	_____
Name of Patient/Participant	Signature	Date
_____	_____	_____
Name of Person taking consent	Signature	Date
_____	_____	_____
Chief Investigator	Signature	Date