Prediction of adverse perinatal outcomes following induction of labour

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Thesis submitted for PhD by Portfolio

Canterbury Christ Church University

DECLARATION

This thesis entitled 'Prediction of adverse perinatal outcomes following induction of labour' has been composed by me, Magdalena Fiolna, and the work in this thesis is my own. This research project was composed by me with advice from my academic supervisor, Professor Akolekar.

From February 2014 until September 2016, I undertook a research fellowship under the supervision of Professor Kypros Nicolaides supported by a grant from the Fetal Medicine Foundation (FMF). In March 2014, I commenced work as a research fellow at the Medway Fetal and Maternal Medicine Centre (MFMC) to pursue my FMF fellowship. Since then, I cooperated closely with Professor Akolekar, and I expressed an interest in undertaking my own research project under his supervision with the aim of pursuing a PhD at Canterbury Christ Church University. I was interested in conducting a study on pregnancy outcomes following induction of labour (IOL). This is because the rates of IOL are rising but there is no robust evidence regarding whether adverse perinatal outcomes and a successful IOL can be predicted prior to starting the process. Since March 2016, I worked with my supervisor, Professor Akolekar, to design the study protocol and liaised with the National Ethics Committee to ensure the project was ethically approved. In addition, I worked closely with the Research and Development Department to keep study documents and site-file up to date with relevant paperwork and substantial amendments whenever necessary. I registered for the PhD with Canterbury Christ Church University in September 2016 to prospectively

report the results of my project within my portfolio and publish it in a peer-reviewed journal. The study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116) who were not involved in the study design, the collection, analysis and interpretation of data, or in the writing of the articles for publication for this thesis.

My contribution to the study consisted of contributing to writing the study protocol, patient information leaflet, consent forms and setting up a Pre-Induction Clinic (PIC) at MFMC. I started the recruitment of patients for this study on the 1st of May 2016 and continued until the 31st of July 2018. I was personally responsible for ensuring that the PIC was running efficiently to ensure appropriate collection of clinical data in keeping with data protection guidelines. I was also responsible for ensuring that research blood samples were stored appropriately at -80 degrees Celsius according to research protocols and for maintaining a database of stored research samples throughout the study period. I obtained pregnancy outcomes and ensured that the outcome measures were accurately coded in the research database by reviewing obstetric records of women participating in this study. I carried out the statistical analysis for the studies in this thesis under the supervision of Professor Akolekar. I presented the preliminary results of the study at the 16th World Congress in Fetal Medicine in Ljubljana, Slovenia and I prospectively published scientific articles in peer-reviewed journals. I also conducted robust literature searches for reviews of published studies and wrote and composed this thesis. This work has not been

previously submitted, in part or whole, for consideration for any other degree or professional qualification.

ABSTRACT

Induction of labour (IOL) is one of the most common obstetric procedures which is carried out in 20-30% of pregnancies. More than a third of women having IOL will need either an instrumental delivery or a caesarean section. Induction will fail for approximately 10% of women who undergo the process. The number of indications for IOL have increased in the last few years with guidelines from professional bodies recommending induction for a range of obstetric and medical complications. This has a significant impact on the capacity and flow on antenatal wards and delivery suites across the country. There are currently no effective methods that can accurately predict the success of IOL.

The current method for assessment prior to IOL includes a vaginal examination to assess the Bishop Score, which is an objective way of defining the extent of cervical ripening. There are other methods described in the current literature such as the measurement of cervical length, posterior cervical angle and more recently the angle of progression (AOP), head to perineum distance (HPD) and cervical compression index (CCI). There is also some evidence that biochemical markers such as placental alpha macroglobulin-1 and fetal fibronectin may predict the onset of labour. This has been used in management of patients with threatened preterm birth. However, there is

no composite model for the accurate prediction of adverse maternal or neonatal outcomes following IOL.

The main objective of this thesis is to examine which factors amongst maternal demographics and components of obstetric history, biophysical and biochemical markers, are altered in women who have adverse outcomes following IOL. I propose to develop a model that will accurately predict the risk of caesarean section for failure to progress or for suspected fetal distress using a combination of maternal and fetal factors measured at a pre-induction clinic (PIC). This model would be of significant benefit in counselling women prior to IOL.

ACKNOWLEDGMENTS

This dissertation is based on the study I carried out whilst working at Medway Fetal and Maternal Medicine Centre as a research fellow for the Fetal Medicine Foundation and subsequently as a trainee in Obstetrics and Gynaecology. The study presented here was carried out between May 2016 and July 2018. It would not have been possible to complete the study and this dissertation without the support and advice of the following people.

First and foremost, I would like to extend my sincere gratitude to Professor Ranjit Akolekar, without whose vision, guidance and support, this study would not have been possible. I feel extremely fortunate not only to have been trained in research, academic and clinical skills at one of the world's best centres for Fetal Medicine but also to have been able to work closely with Professor Akolekar and Professor Nicolaides on various research projects. Their passion, dedication and above all commitment have been a constant source of inspiration and motivation for me. I hope that I am able to imbibe in good measure not only academic and clinical skills but more importantly, the extraordinary work ethic that I have witnessed over the years. In particular, I am grateful to the support and timely advice from my supervisor, Professor Ranjit Akolekar as he helped me set pragmatic deadlines and gave prompt advice, criticism and appropriate supervision whenever needed to enable me to submit this dissertation in a timely fashion.

This study would also not have been possible without the funding support from the Fetal Medicine Foundation (Registered Charity: 1037116). The charity has a long-standing tradition of supporting high-quality research and training in Fetal Medicine and it is because of this ethos and infrastructure that it was possible to accomplish these studies. I am also very grateful to all my research fellow colleagues who believed in the same principles of academic research and helped support these ongoing studies by not only recruiting patients for the prospective studies but by contributing to doing ultrasound scans, taking detailed medical histories and where necessary samples for research. I am particularly grateful to my colleagues Mr Alex Frick, Dr Mirian Machuca and Dr Vera Kostiv who were always there for help, support, and encouragement.

These studies would also not have been possible without the understanding and patience from my family. I am grateful to my best friend and partner, Matt without whose support, I would never have been able to give this work the dedication and concentration it deserved over the years.

Above all, I am enormously grateful to all the women who participated in this research. It is because of their remarkable altruism and desire to support the cause for research to improve women's health, that such studies are even possible. I am privileged that their consent allowed me to undertake this research.

PORTFOLIO

This body of work contains three elements required for my PhD portfolio.

Learning plan and strategy: This is described in Chapter 3 entitled "Material and Methods" and provides information about study population, study design and protocol, ethics approval, patient information leaflet and consent form that were used in the Pre-Induction Clinic.

Presentations and publications: This is included in Chapter 2, which contains a list of outputs produced during my PhD program at Canterbury Christ Church University, including an international oral presentation entitled "Pre-Induction prediction of Caesarean section for failure to progress" (Chapter 4 and 5) and two scientific publications (Chapter 6 and 7) published in a peer-reviewed journal *Ultrasound in Obstetrics & Gynecology (UOG)*, the official journal of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) with an Impact Factor of 7.299. Full text of these peer reviewed publications is available in Appendix VI and VII.

Synthetizing commentary: This includes a comprehensive literature review incorporated into Chapter 1 as well as Chapter 8, which outlines the conclusion and summary.

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ABBREVIATIONS

ACOG	American College of Obstetricians and Gynaecologists
AGA	Appropriate for gestational age
AOP	Angle of progression
APH	Antepartum haemorrhage
ARM	Artificial rupture of membranes
AUROC	Area under receiver operating characteristic curve
BMI	Body Mass Index
BS	Bishop score
CI	Confidence Interval
CS	Caesarean section
CTG	Cardiotocography
CRF	Case report form
CQC	Care Quality Commission
DM	Diabetes Mellitus
DR	Detection Rate
DV	Ductus Venosus
FD	Fetal Distress
fFN	Fetal Fibronectin
FGR	Fetal Growth Restriction
FMF	Fetal Medicine Foundation
FNR	False Negative Rate
FPR	False Positive Rate

FTP	Failure to progress
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
HPD	Head-to-perineum distance
ICP	Intrahepatic cholestasis of pregnancy
IOL	Induction of labour
LGA	Large for gestational age
MCA	Middle Cerebral Artery
MgSO4	Magnesium sulphate
NICE	National Institute of Clinical Excellence
NICU	Neonatal Intensive Care Unit
OASI	Obstetric anal sphincter injury
OC	Obstetric cholestasis
OR	Odds Ratio
PAMG-1	Placental Alpha Macroglobulin -1
PAPP-A	Pregnancy Associated Plasma Protein-A
PI	Pulsatility Index
PIH	Pregnancy induced hypertension
PLGF	Placental Growth Factor
PPH	Postpartum haemorrhage
PV	Per Vaginam
RR	Relative Risk
SCD	Sonographic cervical dilatation
SD	Standard Deviation

SGA	Small for gestational age
SVD	Spontaneous vaginal delivery
sFLT-1	Soluble fms-like Tyrosine Kinase-1
TPUS	Transperineal Ultrasound Scan
TVUS	Transvaginal Ultrasound Scan
UA	Umbilical artery
UK	United Kingdom
USA	United States of America
USS	Ultrasound Scan
WHO	World Health Organisation
VD	Vaginal delivery
VE	Vaginal examination

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Appendix II: Ethical approval for study from NHS Health Research Authority (HRA)

Appendix III: Patient information leaflet.

Appendix IV: Patient consent form.

Appendix V Case record form.

Appendix VI: Full text of my article "Prediction of adverse perinatal outcomes by the cerebroplacental ratio in women undergoing induction of labour" published in *Ultrasound in Obstetrics & Gynaecology*.

Appendix VII: Full text of my article "Prediction of adverse perinatal outcomes by serum placental growth factor and soluble fms-like tyrosine kinase in women undergoing induction of labour" published in *Ultrasound in Obstetrics & Gynaecology*.

Chapter 1

INTRODUCTION &

REVIEW OF LITERATURE

1 CHAPTER 1: INTRODUCTION & REVIEW OF LITERATURE

1.1 OVERVIEW

1.1.1 Development and rationale for the study

Induction of labour (IOL) is a common obstetric procedure and is carried out in approximately 25% of pregnancies (NICE 2008, ACOG 2009, Mealing *et al.*, 2009). There is evidence that more than a third of women having IOL will need either an instrumental delivery or caesarean section (CS) (NICE 2008). Women undergoing IOL should be provided with accurate and personalised information about not just the risks and benefits when undergoing the procedure, but also the potential likelihood of a successful vaginal birth. However, in current clinical practice there are no models or algorithms that provide women with such information. This was the rationale for setting up a Pre-Induction Clinic in which women who are offered IOL would also be offered a clinical review with the aim of collecting data that will help to develop a model that could provide women with a personalised chance of success following this procedure.

The aim of my study was to create this predictive model based on the following maternal and pregnancy characteristics; transabdominal ultrasound assessment of fetal weight; amniotic fluid and Doppler studies; transvaginal assessment of cervical length and posterior cervical angle as well as novel transperineal assessment including the

head to perineum distance and angle of progression. This was covered by the two nested studies which included the data extracted from a larger prospective observational study carried out in Medway Maritime Hospital from May 2016 until May 2018. See Appendix 1. My study, and it's objectives evolved to include not just the prediction of successful vaginal birth but also the prediction of adverse perinatal outcomes such as caesarean section for failure to progress (Chapters 3 and 4).

As the prospective study progressed, I added the prediction of a further set of adverse pregnancy outcomes as surrogate measures which included caesarean section for fetal distress, low cord blood pH, low 5-minute Apgar score, admission to neonatal intensive care unit (NICU) for over 24 hours and hypoxic ischaemic encephalopathy (HIE). This resulted in two more nested studies predicting the above based on biophysical markers [cerebroplacental ratio (CPR)] and biochemical markers [placental growth factor (PlGF) and soluble fms-like tyrosine kinase (sFLT) (Chapters 6 and 7).

1.1.2 Literature review methods

To obtain the relevant information and choose adequate evidence to support my study, I performed a literature review which involved the use of medical databases such as the National library of Medicine (NLM-Pubmed), Google Scholar, CINHAL and EMBASE. I did not restrict my literature search to any particular dates and searched NLM-PubMed and Google Scholar from inception.

The set of key words I used for my literature search included “successful induction of labour”, “failed induction of labour”, “prediction of caesarean section for failure to progress”, “transperineal ultrasound scan”, “placental angiogenic syndrome”, “cerebroplacental ratio”, “PLGF to sFLT-1 ratio”. I supplemented my literature review and discussion with searching using more specific key words as the chapters dictated.

My aim was to include the highest possible level of evidence and I followed the standard guidance regarding the grade and level of scientific evidence. Meta-analysis and systematic reviews of randomised controlled trials (RCT) constituted grade 1A and level 1 evidence whereas level 4 was evidence from expert opinions. Unfortunately, due to the nature of the research question, no RCTs were identified. Most studies included, were observational studies, either retrospective or prospective and constituted level 2 or 3 evidence. I also analysed guidelines and recommendations from national professional bodies such as the National Institute of Clinical Excellence (NICE) and Royal College of Obstetricians and Gynaecologists (RCOG) as well as international professional bodies such as the American College of Obstetricians and Gynaecologists (ACOG) and the World Health Organisation (WHO). In summary, I reviewed full manuscripts of 350 citations, the vast majority of which formed my literature review.

1.1.3 Definition

Induction of labour (IOL) is a medical procedure or treatment which artificially stimulates uterine contractions before the spontaneous onset of labour, with the goal of achieving a vaginal delivery (NICE 2008) (Lueth et al., 2020). IOL is offered to women for whom vaginal birth is safe, and is the most appropriate and acceptable mode of delivery (Marconi, 2019). Additionally, there should be a clear advantage to shortening the pregnancy with an intention of reducing maternal and neonatal morbidity and mortality (Coates et al., 2020). The benefits of labour induction should overrun the potential risks associated with this procedure and should be judged by an experienced clinician. The risks and benefits of prompt delivery versus awaiting the spontaneous onset of labour should be carefully weighted and discussed with each patient (WHO Guidelines, 2011).

Definitions of a successful IOL vary, the same is true for a failed IOL. Most authors define successful labour induction as a process which results in a vaginal delivery within 24h (Pandis et al., 2001; Rane et al., 2004; Rane et al., 2003). Others, believe that achieving a vaginal delivery, spontaneous or assisted, regardless of the timeframe, should be used when defining a successful IOL (Marconi, 2019). Often, in clinical practice, a transition into the active stage of labour, when a woman reaches cervical dilatation of ≥ 4 cm, is sufficient to define labour induction success. This way, there is a clear separation between arrested labour also known as a failure to progress and a failed or unsuccessful IOL.

Women's perceptions and opinions about IOL should be taken into consideration during counselling. Any decision on IOL should be clearly justified and carried out after detailed discussion with a woman and her family. This should include the clinical reasons for IOL, an alternative management plan, description of the whole process as well as possible risks, benefits, and complications. Women should be included in decision making and their wishes should be respected. The feeling of losing control over their body is the most common complaint amongst women undergoing any medical procedures during delivery (Coates et al., 2019).

Currently, women are counselled about IOL, and its possible outcome based on the clinician's experience and the statistical chances of success or failure. However, there are no effective methods which would help accurately predict an individual outcome of labour induction for a particular woman. As obstetricians, we are concerned not only about reaching the stage of successful vaginal delivery but also how safe the whole process is for a mother and her baby. Therefore, maternal, and neonatal outcomes following IOL are even more important than the effectiveness of a particular induction agent (NICE 2008).

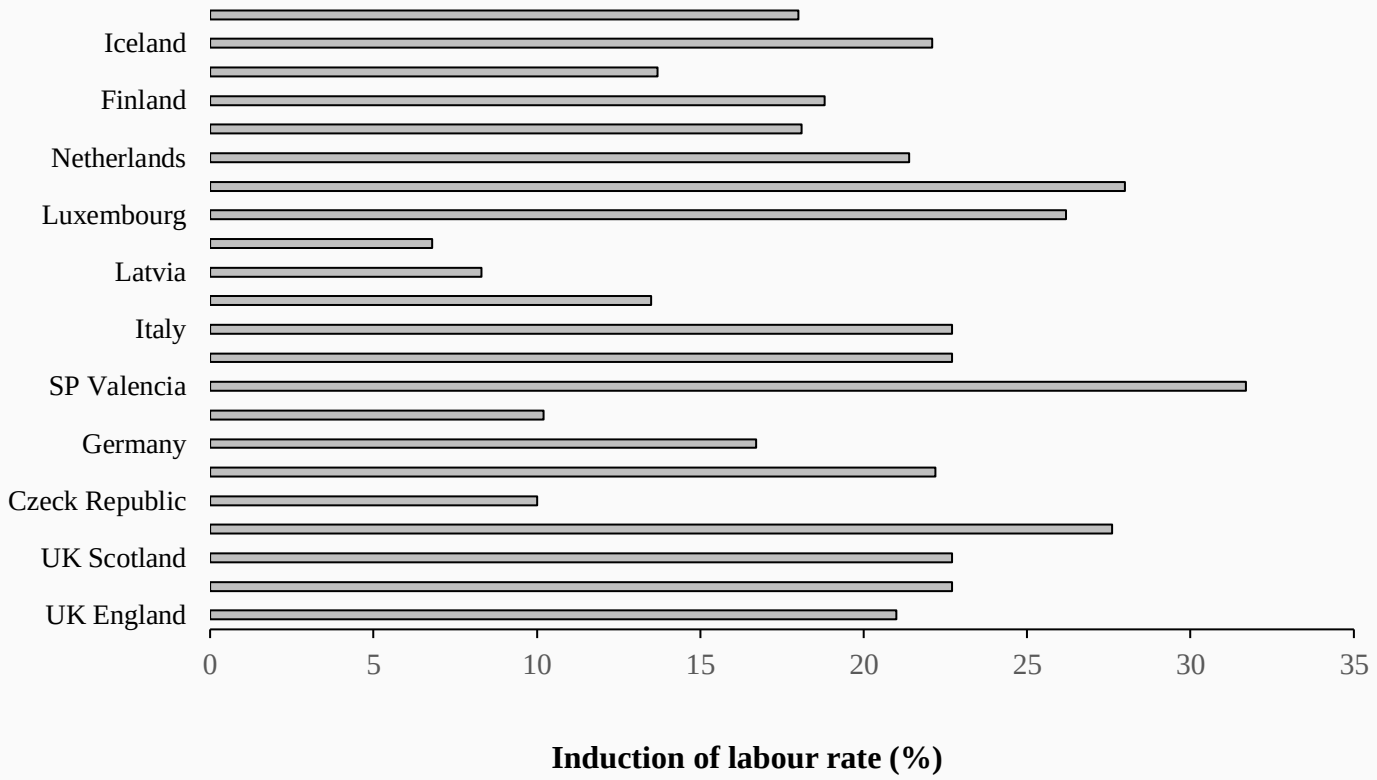
1.1.4 Induction of labour rate

Labour induction is one of the most common obstetric procedures and it is carried out in 25% of all pregnancies worldwide (NICE 2008, ACOG 2009) (Kang et al., 2010).

The number of women whose labour is being induced rises every year and this trend seems to continue as guidelines from various professional bodies recommend IOL for a range of medical and obstetric reasons including post-date pregnancies, hypertensive disorders, diabetes, placental insufficiency leading to fetal growth restriction, multiple pregnancies and many others.

According to a European Perinatal Health Report, there is significant discrepancy in the IOL rate between countries and even centres within the same country (EPHR 2010) (Figure 1.1). Another group compared IOL rates between various countries in Europe and the USA in 2013 and again, the differences were striking (Seijmonsbergen-Schermers et al., 2020) (Figure 1.2 and 1.3). In the UK, approximately 20% of women went through an IOL in 2006 and 2007 and this number increased to 31.6% in 2017 and 2018. There was an increase from 29.4% in 2017 to 31.6% of all pregnant women undergoing the procedure in 2018. 21% of these women needed an instrumental delivery and 22% required an emergency caesarean section (CQC 2019). It is estimated that one in ten women undergoing IOL will never reach an active phase of labour after one cycle of treatment, which is defined as a failed induction. Those women will need either a further attempt to induce labour or an operative delivery via caesarean section. The decision is then made by a clinician based on maternal wishes.

Figure 1.1 European Perinatal Health Report on Induction of labour rates by country



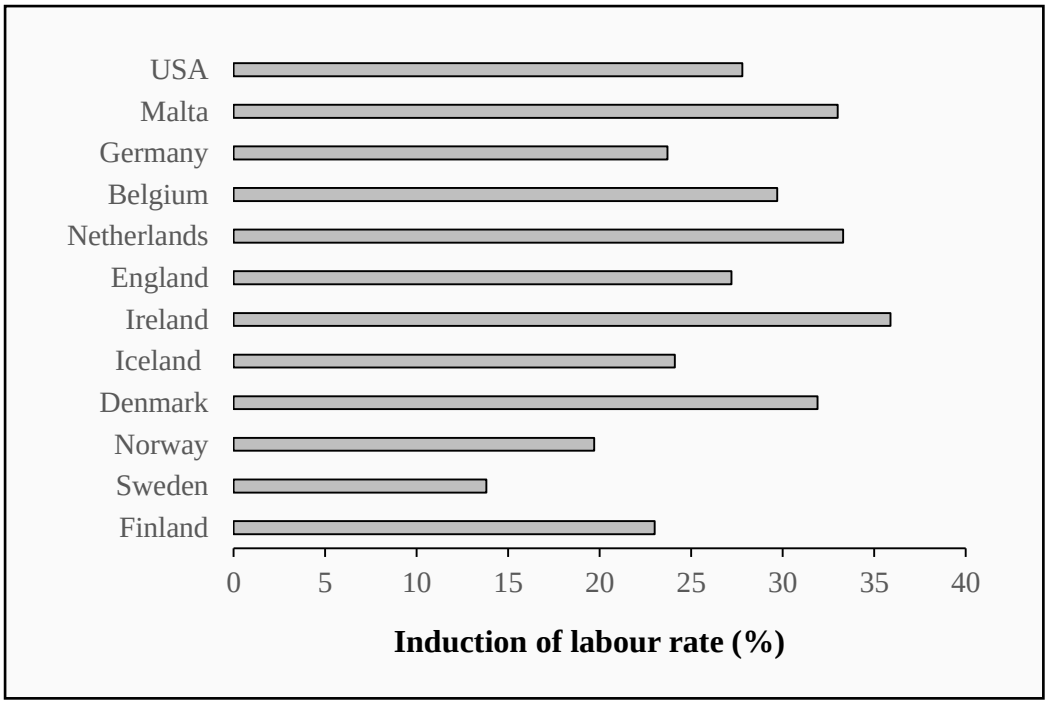


Figure 1.2 Induction of labour rates in Europe and United States

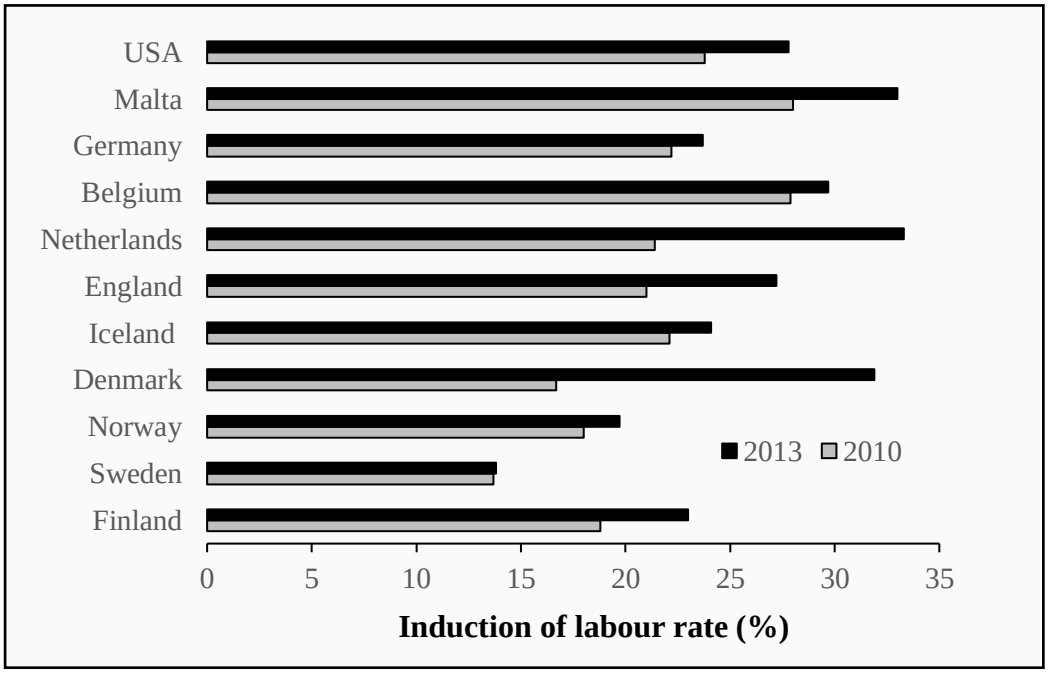


Figure 1.3 Comparison of induction of labour rates in Europe and United States

Labour induction puts a strain on already busy antenatal wards and delivery suits across the country, not only in terms of the workload it creates but also its economic implications (Garcia-Simon et al., 2016). IOL may significantly impact on a woman's experience of birth which often gets overlooked (Coates et al., 2019). A survey of women's experience of maternity care published in the CQC report in 2019, found that patients undergoing IOL request epidural analgesia more commonly (47%) than spontaneous labourers (19%), as the process is usually prolonged and less efficient. Additionally, these women use intramuscular opioid injection more frequently (31% vs 20%). Women who are induced, are rarely able to use water for pain relief in the early stages of labour or deliver in the pool (7% vs 29%). (Figure 1.4)

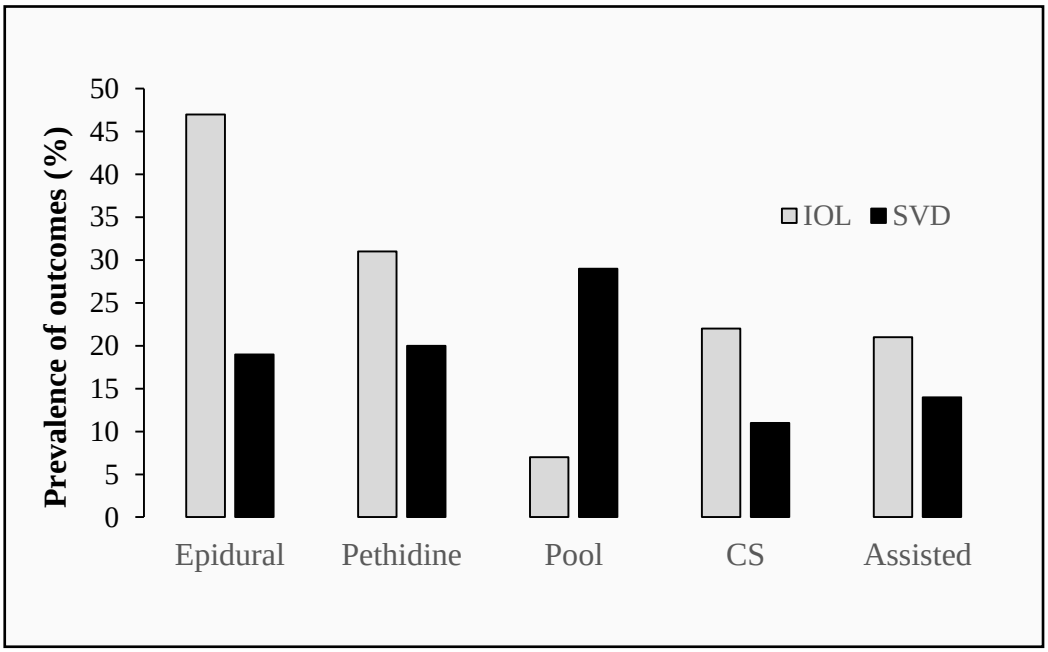


Figure 1.4 Outcomes following IOL vs SVD according to CQC's 2019 survey

Based on the above statistics, it becomes clear that IOL affects a significant proportion of women and has a major impact on perinatal outcomes. Therefore, it is important to carry out clinical research which helps us establish more efficient, safer and acceptable methods of IOL or attempt to predict which pregnancies are likely to have a higher proportion of adverse outcomes such as failed IOL or CS. Accurate prediction of a patient's outcome could potentially improve not only clinical decision making but also increase patient's satisfaction and potentially reduce the cost for the NHS.

1.2 Historical aspects of Induction of labour

IOL was first described in ancient Greece by Hippocrates who established a technique of mammary nipple stimulation to initiate uterine contractions. The above practice was based on the premise that the stimulation of nipples prompts the posterior pituitary gland to release the hormone oxytocin, which also acts on the uterine myometrium to cause contractions (Champetier de Ribes C. 1888). In the second century, Soranus of Ephesus, another Greek physician, described amniotomy, also called an artificial rupture of membranes (ARM) as a method to induce and enhance labour contractions (Baumgarten, 1976). There are no references to newer methods for IOL until the 17th and 18th century, when mechanical, electrical and chemical methods for cervical dilatation were suggested (Donald, 1979). In 1756 at a meeting in London, obstetricians and midwives discussed the ethics and effectiveness of IOL, a leading male midwife, Thomas Denman, advocated ARM as an IOL method for contracted pelvis, which was called the 'English method' (Donald, 1979; Dunn, 1992). In later

years, there were suggestions for electricity to be used for dilatation of the cervix, an idea which was abandoned. Mechanical methods in the form of rubber tubing were considered by Barnes in 1861. Scanzoni in 1856 used a hot carbolic acid douche but this was also subsequently abandoned. Around the same time, Kraus introduced bougies for the mechanical dilatation of the cervix, but these were not considered safe due to their association with sepsis and haemorrhage (Donald, 1979)

The only method to have stood the test of time was the 'English method' of ARM proposed by Thomas Denman which was widely used in England before being implemented elsewhere. In 1845, Edward Murphy, Professor of Midwifery at University College London, wrote that IOL was one of the greatest improvements of modern practice and suggested that the methods in vogue at the time were ARM, direct irritation of the uterus by insertion of a sponge tent, use of ergot alkaloids, repeated use of enemas and at times chloroform (Murphy EW 1845; Brunton J., 1869).

The introduction of oxytocin for IOL started with William Blair Bell in 1909, who reported the effects of pituitary extract "Pituitrin", on a rabbit uterus. It was reported that Pituitrin lone could not induce labour but was proven effective when used with ARM (Blair Bell W., 1915). In 1928, the two components of Pituitrin, oxytocin and vasopressin, were separated at the laboratories of Parke Davies, who named them "Pitocin" and "Pitressin". Intravenous Pitocin was used for IOL in Britain and the USA until the late 1940s (Driscoll WJ et al., 1948). Subsequently, a team at Sandoz synthesised an identical version of Pitocin, called "Syntocinon", which was hailed as

a major advance in Britain and began to be used by intravenous infusion for IOL, a practice still prevalent today (Drife J, 2021).

In the mid-20th century, prostaglandins were discovered and studies in 1968 demonstrated that an intravenous infusion of prostaglandin F2α (PGF2α) can lead to IOL (Hillier et al., 1968). During 1960-70s, other prostaglandin analogues, PGE1 and PGE2 were developed in the form of gels and pessaries, which were reported to be safe and effective (Embrey MP 1970; Hillier et al., 1974).

1.3 Methods of induction of labour

Bishop score assessment via vaginal examination prior to IOL has been an established practice to define the extent of cervical ripening. Based on this score, the adequate method of induction as well as the acting agent, are chosen. There are other methods described in the scientific literature, such as an assessment of factors in obstetric history, maternal demographics, fetal biometry, measurement of cervical length, cervical dilatation on ultrasound, posterior cervical angle and more recently the angle of progression (AOP), head to perineum distance (HPD) and cervical compression index (CCI). There is also some evidence from the management of threatened preterm labour that biochemical markers such as placental alpha macroglobulin-1 and fetal fibronectin may predict the onset of labour. However, there is no composite model that combines information from maternal factors such as, biophysical ultrasound

measurements and biochemical markers to develop a model for accurate prediction of successful IOL.

There are several different methods of IOL. Based on a digital vaginal examination and Bishop score assessment, the cervical ripening status is assessed. If the cervix is 'favourable' (Bishop score ≥ 6), an artificial rupture of membranes can be undertaken, followed by an augmentation of labour with oxytocin if required. Women with a Bishop score of ≥ 8 have a similar chance of achieving vaginal delivery after induction as women presenting in spontaneous labour (Levine, 2020). Women with a low Bishop score should be offered cervical ripening agent to reduce the risk of a failed induction. This can be done either with mechanical cervical dilators or by using pharmaceutical products containing prostaglandins (Stephenson & Wing, 2015).

1.3.1 Mechanical methods of induction of labour

Mechanical methods of IOL were the first ones to be developed. They appear to have less side effects and could potentially improve maternal and neonatal outcomes (de Vaan et al., 2019). Generally, the catheters and rods used for mechanical cervical dilatations are cheaper, easier to store and preserve than pharmaceutical agents (Jozwiak et al., 2012).

Single balloon catheter

The Foley catheter was originally designed in 1929 by Frederic Foley. It is a soft, flexible tube which is passed through the urethra into the bladder to drain urine into a

collection bag (Figure 1.5). It is the most common type of indwelling urinary catheters. There are plenty of indications for its use, especially in urology. An unconventional, but well researched use of the Foley catheter is transvaginal insertion into the cervix for cervical ripening stimulation (Levine et al., 2016).

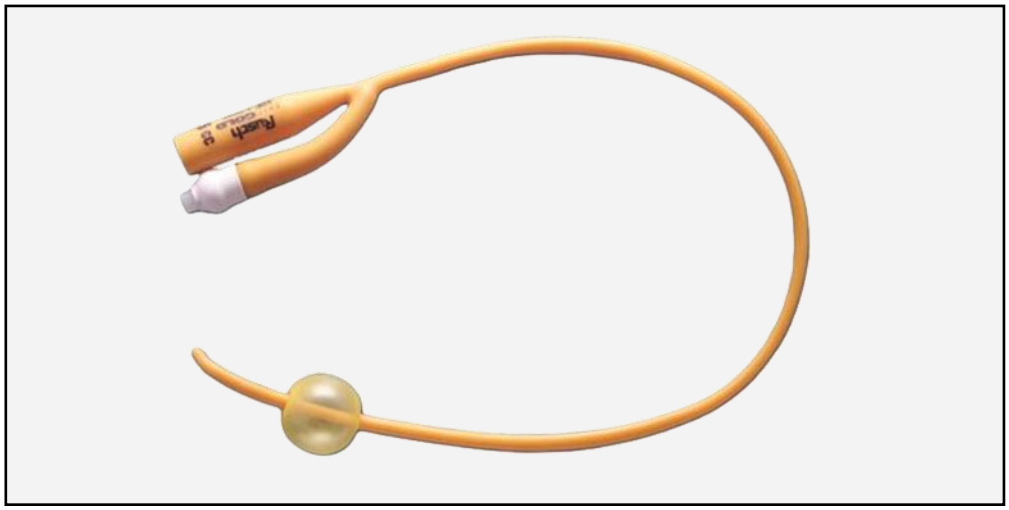


Figure 1.5 Single balloon catheter – Foley catheter

Women undergoing IOL with a Bishop score ≤ 6 or a cervix dilated less than 2 centimetres, can be offered this form of stimulation. A size 16-18F Foley catheter is normally used with a 30cc balloon. The insertion is relatively easy and can be performed during digital vaginal examination or by using a speculum to visualise the cervix (Levine et al., 2016). The catheter bulb is placed above the internal cervical os, inflated with 30 to 60ml of normal saline and placed under tension to create a greater pressure on the cervix (Saad et al., 2019). Inflation to 60ml rather than 30ml seems to shorten the induction to delivery interval and dilates the cervix further without any

adverse effects on neonatal or maternal morbidity. The frequency of caesarean section is not affected by a balloon inflation (Delaney et al., 2010).

This mechanism of action relies on the internal pressure applied to the cervix by the device which directly stretches the lower uterine segment and causes an indirect endogenous prostaglandin release (Keirse et al., 1983; Liu et al., 2019). Apart from the local effect, there seems to be an involvement of neuroendocrine reflexes such as the Ferguson reflex, which may cause uterine contractions in some (Krammer & O'Brien, 1995). The Foley catheter seems to be a safe method of IOL in women with a history of previous caesarean section who wish to achieve a vaginal delivery. The safety of its use was evaluated in a large study which has proven that the Foley catheter does not increase the risk of scar dehiscence or uterine rupture (Katz Eriksen et al., 2019).

In women who were offered IOL beyond their due date with otherwise uncomplicated pregnancies, the Foley catheter seems to be a cost-effective method with high patient satisfaction (Patabendige & Jayawardane, 2017). Mechanical induction with a balloon seems to be as effective as vaginal prostaglandin E2 with a better safety profile. Both, oral and vaginal misoprostol, seem to work better for cervical ripening and labour induction overall. However, their safety profile is either unclear, based on studies included in the Cochrane review, or it remains inferior when compared to a single balloon catheter (de Vaan et al., 2019). Mechanical methods of IOL reduce the risk of uterine tachysystole accompanied by the signs of fetal distress on cardiotocography,

known as hyperstimulation (Chen et al., 2016; Jozwiak et al., 2012). In addition, when compared to augmentation of labour with oxytocin, they reduce the risk of caesarean sections. However, the caesarean section rate is similar for mechanical and pharmacological methods using prostaglandins (Jozwiak et al., 2012).

Double balloon catheter

The Cook balloon is a specially designed product for cervical stimulation during IOL. Unlike the single balloon Foley catheter, the Cook device has two balloons – uterine and vaginal. The uterine balloon works similarly to the Foley catheter applying pressure to the lower uterine segment causing its stretch and localised prostaglandin secretion. The vaginal balloon adds pressure from below the cervix, mechanically squeezing it from both sides. A mean increase in Bishop score by 4.4 units was noted in women who used double balloon catheter in their labour induction process (Atad et al., 1991).

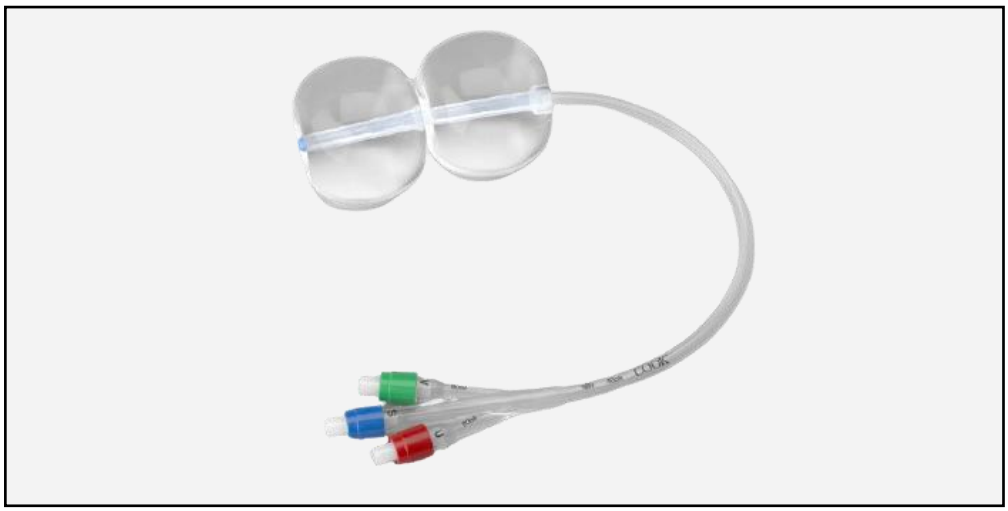


Figure 1.6 Double balloon catheter – Cook® cervical ripening balloon. (Reprinted with permission from Cook Medical)

The insertion process requires a direct visualisation of the cervix in a speculum. The distant, uterine balloon is inflated first with 80 ml of normal saline. Subsequently, the vaginal balloon is inflated with a similar amount of liquid. In my personal experience, the inflation of the vaginal balloon to 20ml at the start of the procedure, prevents the catheter misplacement. The device does not require the application of any tension. Some patients report discomfort during uterine balloon inflation, but this is usually temporarily. Generally, this method is well tolerated by the vast majority of patients. The pain score is significantly lower for the Cook balloon when compared to IOL with prostaglandins (Lim et al., 2018). Normally, the balloon is removed after 12 hours. However, a spontaneous expulsion is possible. The cervix is usually dilated to about 4 to 5 cm at the time of removal or expulsion.

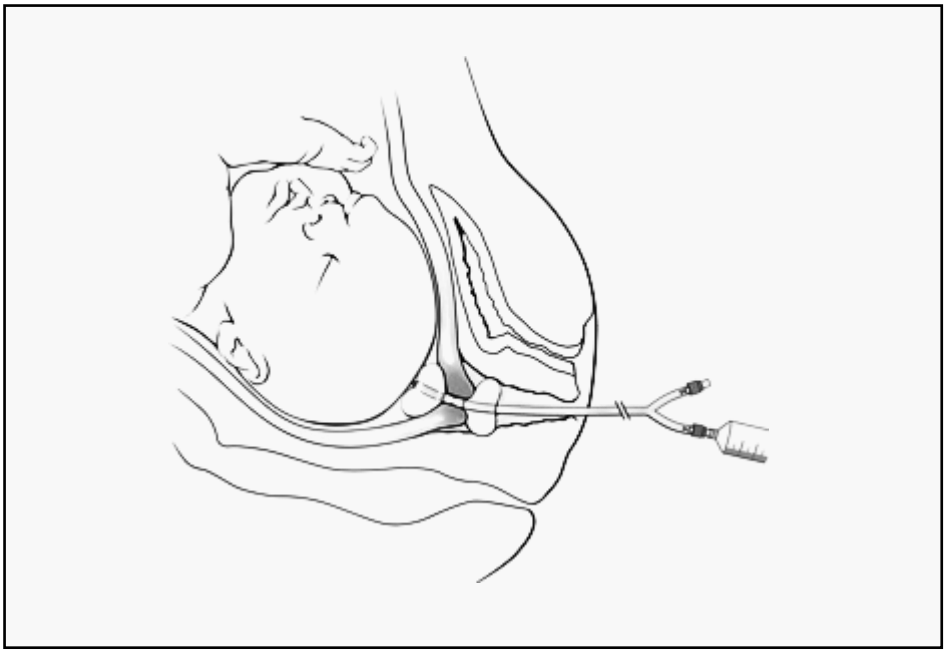


Figure 1.7 Cook® cervical ripening balloon placement. (Reprinted with permission from Medgadget.com)

Both, single and double balloons, have similar safety, patient satisfaction and efficacy profile. However, the single balloon catheter seems to be more cost effective (Liu et al., 2019). Other resources, suggest higher efficacy of a double balloon catheter, especially in nulliparous women (Hoppe et al., 2016)

When compared to pharmacological induction with prostaglandins, the Cook balloon seems to be less effective in achieving vaginal delivery in woman with fetal growth restriction at term. However, the safety profile seems to be the same for both methods (Duro-Gómez et al., 2017a). Similarly, the double balloon catheter failed to reduce the number of unsuccessful labour inductions in nulliparous women in another study (Sulkowski et al., 2019). The advantage of the Cook balloon is the minimal risk of hyperstimulation when compared to misoprostol or amniotomy with subsequent augmentation of labour with oxytocin (Alfirevic et al., 2016). It has the potential of reducing the risk of caesarean section in comparison with oxytocin infusion in women with a low Bishop score (Boulvain, Kelly, et al., 2001).

Synthetic osmotic dilators

Dilapan and currently the upgraded Dilapan-S are synthetic, hygroscopic dilators made of Aquacryl hydrogel (Figure 1.8). The original Dilapan was used in early gestation to prepare the cervix for uterine evacuation. There have been some concerns about its fragmentation, therefore, a better-quality material, Dipalan-S, has been created. It is known to have an improved mechanical property and in 2015 has been approved by

the Food and Drug Administration for use in the late third trimester of pregnancy for cervical preparation (Saad et al., 2019).

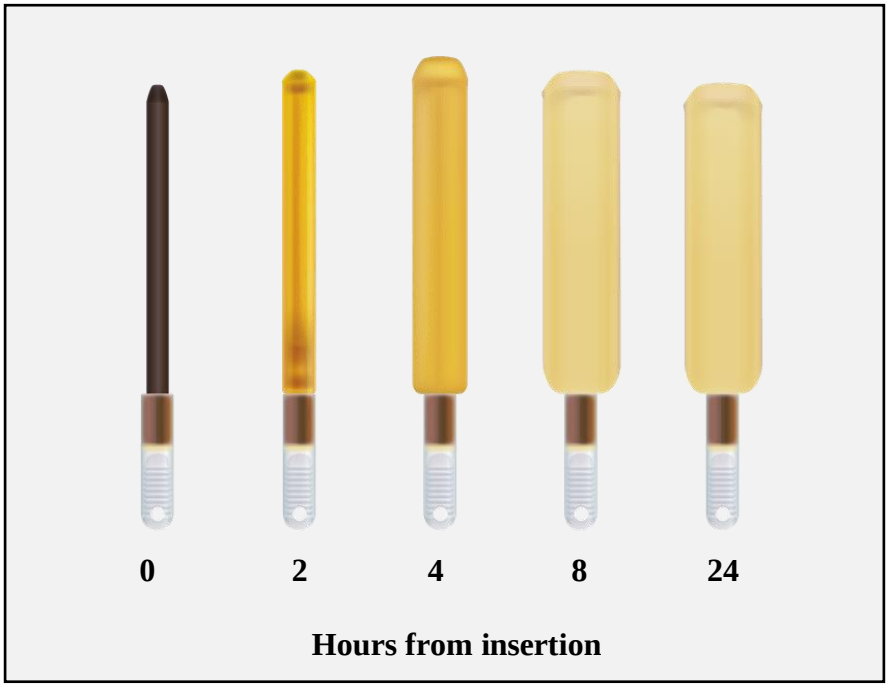


Figure 1.8 Dilapan – S® rods changing their volume overtime. . (Reprinted by permission from NOVUS Pharma Solutions)

Dilapan dilators are rod shaped and designed to be inserted into the cervical canal. They do not require any form of traction and can be contained within the vagina. The hydrogel material, absorbs the moisture from the endocervical glands, causing cell membrane dehydration and softening and eventually mechanical stretching of the cervix, which is followed by a localised prostaglandin surge (Saad et al., 2019). The manufacturer's instructions, encourage insertion of as many rods as possible into the

cervical canal under direct vision using a sterile speculum (Figure 1.9). Dilapan-S rods are then removed after 12 to 24 hours during vaginal examination.

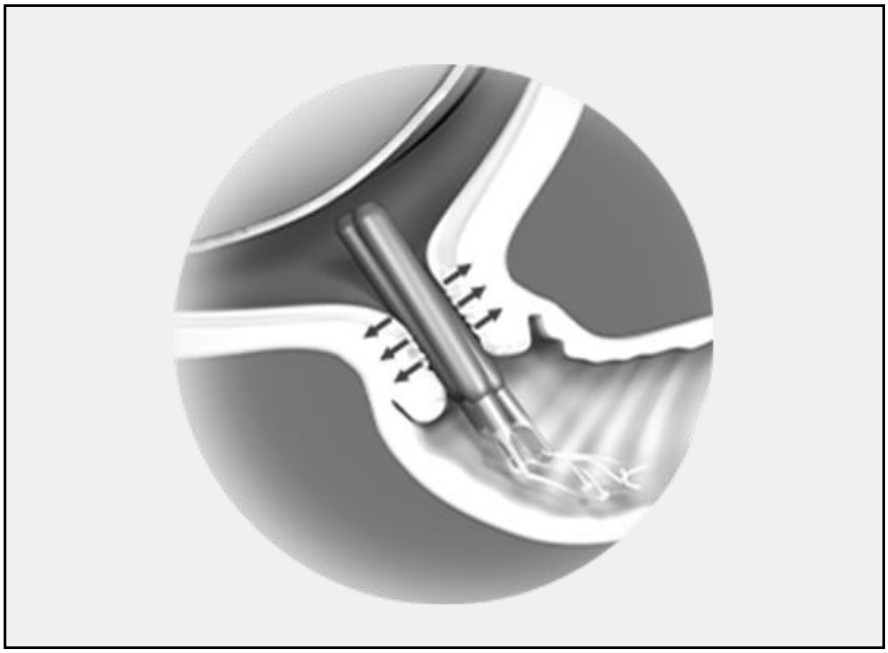


Figure 1.9 Dilapan- S® inserted into the cervical canal. (Reprinted by permission from NOVUS Pharma Solutions)

When compared to a single balloon catheter, Dilapan-S rods are as effective for cervical ripening in women with a Bishop score ≤ 6. Both methods were found to have very minimal adverse effects. In addition, patients seem to prefer Dilapan-S over the Foley catheter as they find it less disruptive to their daily activities (Saad et al., 2019). Overall, synthetic osmotic dilators seem to be an effective method of labour induction with a good safety profile. The rate of maternal and neonatal adverse outcomes is generally very low (Gupta et al., 2018). This method can be used by itself or in

combination with pharmacological methods, possibly increasing the rate of vaginal deliveries and reducing labour duration when combined (Baev et al., 2019).

1.3.2 Pharmacological methods of induction of labour

Prostaglandins are derivatives of arachidonic acid and can be found in many different parts of a human body. Prostaglandins not only play a major part in the physiological process of cervical ripening in the late third trimester of pregnancy, but also increase a smooth uterine muscle contractility (Gilstrop & Sciscione, 2015). Synthetic prostaglandins, which are the analogues of natural isoforms, come in a large variety of forms including oral and vaginal tablets, gel or pessaries (Levine, 2020).

There is good evidence that they increase vaginal delivery rate within 24h of induction and reduce the risk of caesarean section in women without a history of previous operative, abdominal delivery. They are known to reduce the need for subsequent oxytocin infusion to enhance uterine contractions (Kelly et al., 2009; Liu et al., 2014; Thomas et al., 2014). The main disadvantage in their use, is the potential to cause an increased number of contractions known as tachysystole (Levine, 2020) which may result in maternal or fetal distress.

Dinoprostone

Dinoprostone is a prostaglandin E2 analogue. It is the only prostaglandin approved by the Food and Drug Administration for cervical ripening. It comes in several vaginal

formulations including a slow release vaginal insert, pessary or gel (Levine, 2020). Intracervical gel is not commonly used in the UK. Propess ® which is a vaginal insert, contains 10mg of prostaglandin E2 which is slowly released over 24h. It does not dissolve and can be easily removed by pulling on its retrieval tape in case of tachysystole or hyperstimulation. Both, gel and tablet formulations get absorbed over time. It is uncertain by which mechanism of action dinoprostone causes a cervical ripening, however, it is likely due to a local secretion of collagenase leading to collagen degradation (Gilstrop & Sciscione, 2015).

When compared with a placebo, prostaglandin E2 increases the rate of vaginal deliveries within 24h. It also reduces the likelihood of CS for failure to progress by about 10%. On the other hand, the risk of uterine tachysystole leading to fetal heart rate changes with vaginal prostaglandin E2 is three times higher than with placebo. There appears to be equal efficacy of different formulations of prostaglandin E2 including tablets, pessaries, gel and slow-release vaginal inserts. Taking into consideration the variety of measures, there is no clear evidence that prostaglandin E2 impacts on fetal and maternal long term outcomes. (Thomas et al., 2014). Synthetic prostaglandin E2 analogues are expensive compared to misoprostol or balloon catheters and they need to be kept refrigerated. Additionally, they take longer to work (12-24h) when compared to misoprostol (3-4h) (Levine, 2020)

Misoprostol

Misoprostol is a synthetic prostaglandin E1. Originally approved by the Food and Drug Administration for peptic ulcer prevention. Its off-label use for cervical ripening in IOL was approved in 2002 (Levine, 2020).

Misoprostol comes in many formulations and can be administered orally, sublingually, buccally, or vaginally. The dosing regimen differs for each formulation and it is based on different pharmacokinetics (Levine, 2020). So far, the most studied and therefore recommended administration routs are oral or vaginal (Stephenson & Wing, 2015). The Cochrane review however, emphasises preferability of oral versus vaginal misoprostol due to increased risk of hyperstimulation (Hofmeyr et al., 2010).

An undoubted advantage of Misoprostol over other induction agents such as Dinoprostone, is its lower price and pharmaceutical stability when stored at room temperature (Levine, 2020; Stephenson & Wing, 2015). There is conflicting evidence in the literature regarding the most effective method of cervical ripening. Amongst parous women, misoprostol appears to be related to the lowest caesarean sections rate. However, if we take into consideration women who never delivered vaginally before, this rate is similar with all the induction methods including oxytocin, Foley catheter, misoprostol and dinoprostone (Aghideh et al., 2014). Another study reported that oral misoprostol and single balloon catheter are equally safe and effective when used in women with a low Bishop score at term (Ten Eikelder et al., 2016). The general consensus based on systematic review and meta-analyses is that oral misoprostol is the

most effective method in achieving vaginal delivery within 24h and simultaneously reduces the rate of postpartum haemorrhage (Alfirevic et al., 2014). But is also associated with the highest risk of uterine tachysystole or hyperstimulation (Chen et al., 2016) as well as meconium stained liquor (Alfirevic et al., 2014). In clinical practice in the UK, oral misoprostol is only used for labour induction in women who had suffered an intrauterine fetal death (NICE CG 70, 2008).

1.3.3 Membrane sweeping

Membrane sweeping should be offered to women prior to formal IOL (NICE CG 70). It is cheap, safe and effective. It can be easily performed in outpatient settings even in Group B Streptococcus positive women (Heilman & Sushereba, 2015). The number needed to treat is sever, which in the context of labour induction means, that if the membrane sweep is performed in seven women, one of them will avoid a formal IOL (Boulvain, Stan, et al., 2001).

Membrane sweep is a mechanical technique performed during vaginal examination. It requires insertion of one or ideally two fingers into the cervix and application of continuous circular motions to stretch the cervix and detach the membranes from the lower uterine segment. This causes a local prostaglandin surge and promotes cervical softening, effacement and dilatation (Finucane et al., 2020). It is effective from 38 weeks gestation and its efficacy does not depend on timing or number of sweeps performed (Avdiyovski et al., 2019).

Routine membrane sweeping has a potential of decreasing the number of formal labour inductions for post maturity in low-risk pregnancies (Avdiyovski et al., 2019; de Miranda et al., 2006). Unfortunately, these findings were not confirmed in women who wish to undergo a trial of vaginal delivery after caesarean section. In this group, routine membrane sweeping does not seem to be effective in promoting the spontaneous onset of labour (Hamidi et al., 2020).

1.3.4 Artificial rupture of membranes

Artificial rupture of membranes also known as amniotomy is one of the oldest methods of labour induction. It consists of the intentional disruption of amniotic sac continuity by a healthcare professional in order to start or augment labour contractions (Mahdy et al., 2020).

Anatomically, the amniotic sac surrounds the amniotic cavity which contains the fetus, the placenta, and the amniotic fluid. It is a double layer membrane made of amnion and chorion which creates a barrier between the interior of the uterus and the outside world. This barrier should remain intact antenatally and usually ruptures spontaneously in labour (Mahdy et al., 2020). In the context of labour induction, artificial rupture of membranes can be performed in women with Bishop score of ≥ 6 or cervical dilatation of > 1cm. The two most commonly used instruments to perform the amniotomy are, either a rod (Amnihook) or a finger cot (Amnicot) with a small hook at the end. Membranes are palpated during digital vaginal examination and

ruptured with a hook. This is typically followed by the amniotic fluid drainage from the vagina. Care should be taken to ensure there is no umbilical cord coming down into the vagina as a result of amniotomy (Mahdy et al., 2020). In terms of the timing of artificial rupture of membranes, early amniotomy is performed before the onset of contractions to induce labour and late amniotomy can be performed in active labour to augment the strength and frequency of contractions.

Overall, based on the results of a systematic review of literature and meta-analysis, early amniotomy as a part of IOL process, results in a shorter induction to delivery interval and does not carry any additional risks for adverse perinatal outcomes (Kim et al., 2019). Additionally, it does not increase the rate of caesarean sections (De Vivo et al., 2020). However, in special circumstances when the IOL is undertaken in morbidly obese women with BMI ≥40, early amniotomy may increase the rate of caesarean delivery (Pasko et al., 2019).

1.3.5 Augmentation of labour with Oxytocin

Oxytocin is a nanopeptide produced by hypothalamus and stored in the posterior pituitary gland (Gilstrop & Sciscione, 2015). It is released during sexual intercourse, breastfeeding and in labour. Therefore, it plays a big role in reproduction and social bonding between partners as well as between a mother and her baby (Francis et al., 2002).

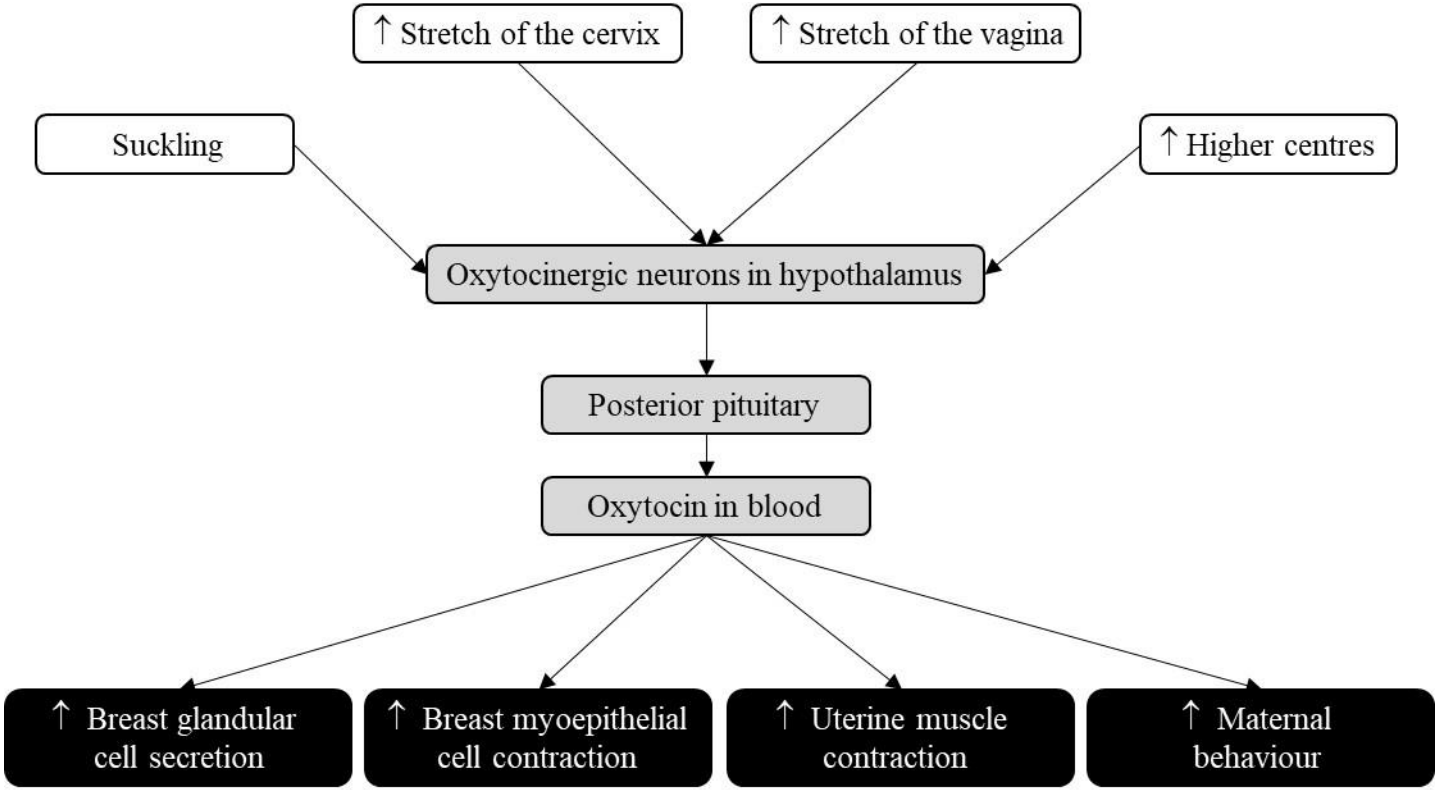


Figure 1.10 Ferguson reflex – positive feedback mechanism

Its action is mediated by specific oxytocin receptors (typical class I G receptors) on myometrial cells (Gimpl & Fahrenholz, 2001). Oxytocin bonds with the class I G receptor and activates the signalling pathway which results in high calcium concentration within the myometrial cell. This leads to a smooth muscle contraction within the uterus (Gilstrop & Sciscione, 2015) (Figure 1.10). An oxytocin surge leading to regular uterine contractions can be a natural consequence of nipple stimulation or as a result of iatrogenic infusion with synthetic oxytocin (Kernberg & Caughey, 2017). Oxytocin does not have any impact on cervical ripening due to the lack of smooth muscle within the cervix. Therefore, it should only be used in women with a favourable cervix and Bishop score of ≥ 6 (Levine et al., 2020) (Figure 1.10).

Augmentation of labour is a process of strengthening contractions in order to achieve an adequate progress in labour and eventually a vaginal delivery. It reduces maternal and fetal consequences of prolonged labour (Kernberg & Caughey, 2017; Nabhan & Boulvain, 2020). A synthesized, exogenous hormone is used, usually in the form of intravenous infusion. The average response to oxytocin is quick and takes between 3 and 5 minutes (Simpson, 2011). However, if the infusion is started in early phases of induction, it may take 10 hours to achieve a cervical dilatation by 1cm. Once the cervix is dilated to 5 cm and effective uterine contractions are present, further dilatation by 1cm should occur in 2 hours (Zhang et al., 2018).

It is estimated that worldwide, half of women in labour undergo augmentation with oxytocin (Zhang et al., 2011). A slow, continuous administration with close

monitoring of the strength and frequency of contractions as well as fetal heart rate monitoring is advised to reduce the risk of complications. The rate at which oxytocin infusion is increased should be at least 30 minutes to minimalize the excessive doses (Simpson, 2011). The most common side effects associated with the use of oxytocin is tachysystole (more than 5 contractions in every 10 minutes), hyperstimulation (tachysystole complicated by fetal heart rate changes) and in rare cases, uterine rupture (Nabhan & Boulvain, 2020).

Oxytocin infusion can shorten labour by approximately 2 hours with no significant adverse maternal or neonatal outcomes (Bugg et al., 2013). High doses of oxytocin when compared to lower doses, reduce the length of labour as well as the rate of caesarean sections for failure to progress, increase the rate of spontaneous vaginal deliveries and chorioamnionitis. However, they increase the risk of hyperstimulation. We need to be cautious about the oxytocin use as there is no long term data on infants outcomes nor maternal satisfaction (Kenyon et al., 2013). Women with history of previous caesarean section should be counselled carefully about the augmentation of labour with oxytocin as it increases their risk of uterine rupture. For these patients, low dose regimen should be used ("ACOG Practice Bulletin No. 205: Vaginal Birth After Cesarean Delivery," 2019).

Additionally, the rate of instrumental deliveries does not seem to be reduced with oxytocin infusion in women with epidural analgesia in labour (Costley & East, 2013).

Summary

There is an ongoing debate on which method of IOL is the best and the consensus has not been reached despite several Cochrane reviews, systematic reviews and meta-analysis being published (Alfirevic et al., 2016; Boulvain, Kelly, et al., 2001; Chen et al., 2016; de Vaan et al., 2019; Jozwiak et al., 2012; Mozurkewich et al., 2011; Vogel et al., 2017). Generally, women with a favourable cervix undergo an artificial rupture of membranes followed by the augmentation of labour with intravenous oxytocin infusion. If the cervix is unfavourable, cervical ripening should be offered, using one of the mechanical or pharmacological methods (Penfield & Wing, 2017). Individual Trusts have developed their own protocols for cervical ripening and IOL. They often differ between the groups of patients taking into consideration their parity, history of caesarean section, and history of prelabour rupture of membranes etc.

1.4 Indications for induction of labour

There is an increasing number of clinical situations when the risks of prolonging the pregnancy in order to await spontaneous onset of labour might be related to adverse maternal or neonatal outcomes (Crane, 2006). While many of the indications for IOL have been supported by a body of evidence, it is not clear how some are beneficial (Coates et al., 2020). In this chapter I will address the most common indications for IOL.

1.4.1 Antepartum haemorrhage

Antepartum haemorrhage (APH) is a significant bleeding from the genital tract during pregnancy (from 24 weeks onwards) or before the end of the second stage of labour (RCOG GTG 63, 2011). The latter is often called an intrapartum haemorrhage. It may have dramatic maternal and/or fetal consequences if it is caused by placental abruption, vasa praevia or placenta praevia. Therefore, these causes should be excluded immediately in all women complaining of vaginal bleeding.

Placental abruption is defined as the separation of the normally developed placenta from the uterine wall prior to delivery (Tikkanen, 2011). It is usually diagnosed clinically based on maternal symptoms including abdominal pain and vaginal bleeding as well as signs of fetal distress if abruption is significant (Downes et al., 2017). Vasa praevia and placenta praevia can be diagnosed on ultrasound. Antenatal diagnosis significantly improves fetal outcomes as it results in planned delivery by an early elective caesarean section prior to the onset of contractions (Zhang et al., 2020). This reduces the risk of painless bleeding episodes. Approximately 50% of all APH episodes are of unknown origin. It complicates about 5% of pregnancies and is diagnosed after exclusion of all previously described placental causes (Bhandari et al., 2014). APH has been found to increase the risk of preterm delivery and has associated complications (Bhandari et al., 2014; Chan & To, 1999). However, it does not increase the risk of fetal growth restriction or stillbirth (Bhandari et al., 2014).

There is no evidence in the literature which suggests the best timing of delivery for women experiencing vaginal bleeding in pregnancy. The Royal College of Obstetricians and Gynaecologists advises careful observation to exclude maternal and/or fetal compromise. If this is achieved and there is no further significant bleeding, then elective preterm delivery should be avoided. If however, a woman presents after completing 37 weeks gestations, reporting an episode of vaginal bleeding, IOL should be considered in order to achieve vaginal delivery and to avoid the potential risk of placental abruption (RCOG GTG 63, 2011).

1.4.2 Hypertensive disorders

Hypertensive disorders are the most common medical conditions complicating pregnancies worldwide. About 10% of all obstetric patients suffer from some degree of hypertension (Pretscher et al., 2020) which includes pre-existing or chronic hypertension, gestational hypertension, preeclampsia and eclampsia (Braunthal & Brateanu, 2019). It is important to monitor blood pressure in pregnancy, diagnose and treat hypertension in order to prevent complications.

Hypertension in pregnancy is defined as blood pressure exceeding 140/90mmHg on two separate occasions and if it is greater than 160/110mmHg it is classified as severe (Braunthal & Brateanu, 2019) ("Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy," 2000) (Table 1.1).

Chronic, also known as essential or pre-existing hypertension is defined as preconception hypertension or if it develops in the first 20 weeks of pregnancy.

- Gestational or pregnancy induced hypertension evolves after 20 weeks gestation and usually normalises up to 42 days post-delivery.
- Preeclampsia is a new onset hypertension after 20 weeks gestation complicated most commonly by proteinuria but also other signs of maternal organ dysfunction or placental dysfunction. Eclampsia is preeclampsia complicated by non-epileptic seizures.
- Chronic hypertension can also be complicated by superimpose preeclampsia or even eclampsia.

Hypertension known before pregnancy or present in the first 20 weeks
Chronic hypertension Essential Secondary White – coat hypertension Masked hypertension
Hypertension arising de novo at or after 20 weeks
Transient gestational hypertension Gestational hypertension Preeclampsia de novo superimposed on chronic hypertension

Table 1.1 ISSHP Classification of the Hypertensive Disorders in Pregnancy (Mark A. Brown et al., 2018)

The above classification has been adopted by obstetric physicians around the world ("ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy," 2019; Braunthal & Brateanu, 2019; M. A. Brown et al., 2018).

Any form of hypertension in pregnancy can result in preeclampsia. About one third of women with gestational hypertension and a quarter of those with chronic hypertension will develop organ dysfunction (Magee & von Dadelszen, 2018; Seely & Ecker, 2014; Sibai et al., 1998). Despite extensive research the pathophysiology of preeclampsia is not fully understood but it is likely a result of systemic vascular endothelial dysfunction (Granger et al., 2001).

Current management focuses on keeping blood pressure within normal limits by using several different types of anti-hypertensives available to pregnant women. The only curative treatment is delivery. In cases of severe, preterm preeclampsia often complicated by fetal growth restriction, delivery by caesarean section is usually indicated (Kehl et al., 2017; Stepan et al., 2015)(NICE NG133, 2019). Women with mild preeclampsia or those who developed the condition late in pregnancy should be offered IOL with the aim of achieving a vaginal delivery (Koopmans et al., 2009) (NICE NG133, 2019).

IOL at 37 weeks onwards reduces the risk of complications and improves maternal outcomes in women even with mild form of hypertensive disorder (Koopmans et al., 2009). Neonatal outcomes following successful IOL versus elective caesarean section

were comparable and vaginal delivery does not have a negative impact on neonatal morbidity or mortality when adjusted for gestational age (Alanis et al., 2008; Kehl et al., 2017; Nassar et al., 1998). Interestingly, IOL in women with preeclampsia when compared to women induced for other reasons is unlikely to influence the caesarean section rate. Their interval from induction to delivery however, seems to be longer and less of them deliver within 48h from the start of induction (Pretscher et al., 2020)

Weeks of pregnancy	**Timing of birth**
<34 weeks	Continuous surveillance – offer MgSO4 +/- steroids
From 34^{+0} to 36^{+6} weeks	Continuous surveillance – steroids if indicated
>37 weeks	Initiate within 24-48 hours

Table 1.2 Timing of birth in women with preeclampsia. NICE CG133.

The National Institute for Health and Care Excellence (NICE) updated its guidance on hypertension in pregnancy in June 2019. It advises postponing the decision on delivery until at least 37 weeks gestation in women with chronic hypertension, unless their blood pressure exceeds 160/110 mmHg or there are any other obstetric indications. The advice is very similar for gestational hypertension. In women suffering from preeclampsia, early delivery is often indicated due to multi-organ failure or uncontrollable blood pressure. Timing and mode of delivery should be individualised. However, if a patient with preeclampsia reaches 37 weeks gestation, IOL should be planned within 24 to 48h (NICE CG133) (Table 1.2).

1.4.3 Gestational proteinuria

Proteinuria is an excessive loss of protein with urine. It is typical for glomerular kidney disease and its level is used to make a diagnosis, follow up and determine therapeutic response (Hladunewich & Schaefer, 2011). Accurate assessment of proteinuria is difficult in pregnancy due to physiological changes such as increased glomerular filtration and baseline membrane permeability as well as decreased protein reabsorption (Chung & To, 2018). The loss of 300mg of protein or more within 24h is significant in pregnancy. The established cut off can be used for diagnosis of abnormal proteinuria. However, the severity of condition should not be determined based on the amount of protein excreted (Lindheimer & Kanter, 2010).

Gestational proteinuria is defined as an excessive urinary protein excretion after 20 weeks of pregnancy. Preeclampsia should always be excluded in these women. Preconception or early pregnancy proteinuria is likely related to a chronic kidney disease (Airoldi & Weinstein, 2007).

Initially, IOL for women with isolated gestational proteinuria was discouraged due to overall good maternal and neonatal outcomes (Airoldi & Weinstein, 2007). However, it is possible that this phenomenon is a part of preeclampsia spectrum and hypertension may subsequently follow (Chung & To, 2018; Morikawa et al., 2009). The higher the level of proteinuria at the moment of diagnosis or the earlier presentation, the greater the risk of developing preeclampsia (Morikawa et al., 2008). A level of 2g/24h was

predictive of this sequence of events. Outcomes worsen for women who subsequently develop hypertension when compared to those who remain normotensive. The mean interval from diagnosis of proteinuria to delivery seems to be 3.8 weeks. Women with proteinuria should be followed up frequently, as quarter may develop some degree of organ disfunction and/or placental insufficiency (Chung & To, 2018). Therefore, IOL at term in these women is not unreasonable and should be considered.

1.4.4 Diabetes mellitus

Diabetes mellitus is the most common pre-existing medical condition in pregnancy. It affects between 6% and 9% of pregnancies. Approximately 90% of these women suffer from gestational diabetes. Type 1 and type 2 diabetes account for the remaining 10% (Bishop et al., 2019). The number of pregnancies affected by diabetes rises worldwide which is partially related to postponing pregnancy to a later age (Bartášková, 2019) but also to the epidemic of obesity and increasing numbers of women with BMI > 30 in reproductive age. This is mostly reflected in rising numbers of diabetes type 2 and gestational diabetes ("14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2019," 2019) for which obesity is one of the most important risk factors. Because of possible maternal and fetal complications associated with all types of diabetes, it is important to adequately plan the pregnancy and follow these patients closely to minimalize the risks. Good glycaemic control decreases the risk of early pregnancy loss, fetal defects, macrosomia and polyhydramnios.

Gestational diabetes is defined as any degree of glucose intolerance which is diagnosed or first manifested in pregnancy ("International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy," 2010). Overall, it poses significantly less risk to the fetus and to the mother compared to pre-gestational diabetes with small differences according to the type ("14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2019," 2019).

The guidance on when and how to deliver women with diabetes in pregnancy is incoherent and most professional bodies recommend delivery between 34 and 39 weeks' gestation depending on glycaemic control (Berger & Melamed, 2014; Caughey & Valent, 2016).

The rationale for IOL has always been prevention of stillbirth and maternal complications, such as increased risk of caesarean section or birth trauma. This has to be weighed against potentially increased neonatal morbidity (Berger & Melamed, 2014). It seems that, neonates of diabetic mothers' benefit from delivery from 37 up to 40 weeks gestation. Neonatal morbidity and mortality are likely to be reduced in cases when elective delivery occurs before 40 weeks gestation. However, it is increased for iatrogenic preterm deliveries (Metcalfe et al., 2020).

Type of diabetes	Timing of birth
DM type 1 or 2 – no complications	Initiate birth between 37^{+0} - 38^{+6}
DM type 1 or 2 – maternal / fetal complications	Initiate birth ≤ 37 weeks
GDM – no complications	Initiate delivery ≤ 40+6
GDM – maternal or fetal complications	Initiate delivery < 40^{+6}

Table 1.3 Timing of birth in women with diabetes in pregnancy. NICE NG3

NICE recommends planned delivery between 37 and 38^{+6} weeks' gestation for women with pre-gestational diabetes, irrespective of its type. Mode of delivery should be individualised. Risks and benefits of IOL versus elective caesarean section should be discussed taking into consideration past obstetric history, fetal size and presence of polyhydramnios. Preterm delivery could be considered in cases of complicated type 1 or type 2 diabetes (NICE NG3). Women with gestational, diet-controlled diabetes should be offered delivery before 40^{+6} weeks gestation. Earlier deliver could be indicated in view of significant maternal or fetal risk factors. If a woman has a history of caesarean birth but wishes to achieve a vaginal delivery, this could be facilitated despite her diabetes, if there are not obstetrics contraindications (NICE NG3).

1.4.5 Fetal defects

Advances in fetal ultrasonographic assessment led to improvement in antenatal diagnosis of many structural anomalies. Approximately 60% of severe congenital defects can be diagnosed during an anomaly scan (Wataganara et al., 2017). Some of

them are so severe that the termination of pregnancy should be offered. Some, however, can be successfully managed in pregnancy or postnatally. Depending on the type of fetal defect and maternal wishes, an individual decision should be made on mode of delivery.

Congenital heart disease

Congenital heart defects are the most common structural birth defects unrelated to chromosomal abnormalities (Dolk et al., 2010; Wataganara et al., 2017). The detection rate of congenital heart disease (CHD) increased significantly in the last 20 years due to improvements in antenatal screening (International Society of Ultrasound in et al., 2013; Peyvandi et al., 2017). Interestingly, neonates diagnosed in pregnancy with major cardiac defects such as hypoplastic left heart syndrome or transposition of the great arteries, are delivered on average one week earlier, with a lower birth weight, than neonates diagnosed after delivery. Neonates diagnosed postnatally are intubated more frequently and have their corrective surgery sooner than those diagnosed in utero. However, this has no impact on their overall survival rate. Fetuses with antenatal diagnosis of CHD are more often delivered by an elective or an emergency caesarean section. Overall, the mode of delivery does not seem to impact the survival rate. Surprisingly, the hospital stay seems to be longer for neonates delivered via caesarean section compared to those delivered vaginally (Peyvandi et al., 2017). Majority of fetuses with cardiac defects can be safely delivered vaginally (Jowett et al., 2014; Wataganara et al., 2017) and elective caesarean delivery does not improve the outcomes in fetuses with such a severe malformation as hypoplastic left heart

syndrome (Peterson et al., 2011). Taking into consideration the above findings, IOL after careful counselling is not unreasonable and could be considered.

Abdominal wall defects

Gastroschisis and omphalocele are congenital abdominal wall defects and one of the most common structural birth defects (Wataganara et al., 2017). Gastroschisis is slightly less common than omphalocele but its incidence rose significantly in the last 20 years and carries a huge cost burden for neonatal intensive care units (Skarsgard, 2016). There has been a lot of discussion about timing and mode of delivery for affected fetuses. There is a theoretical risk of the damaging effect of amniotic fluid to the exposed viscera which has been studied and the attempt to reduce this risk by an early delivery has not been successful (Ergün et al., 2005). Similarly, the detrimental effect of maternal bacterial flora on the bowel following vaginal delivery or reduction in mesenteric blood supply during contractions have been described (Sakala et al., 1993). However, these seem to be theoretical and negligible (Wataganara et al., 2017). Mode of delivery does not seem to affect the paediatric mortality rate, the time when enteral feeding can be started or even length of hospital stay (Segel et al., 2001). Another significant issue which may impact obstetric decision making on mode of delivery, is poor ultrasonographic prediction of fetal weight. Due to altered anatomical landmarks, the abdominal circumference, which is the most important component of the estimated fetal weight calculating formula, is often underestimated. Approximately, only 35% of fetuses delivered by caesarean section for fetal growth restriction and fetal distress, were small for dates after delivery (Fisher et al., 2020).

General consensus is, that abdominal wall defects, especially gastroschisis in genetically normal fetuses is not an indication for an operative delivery. However, every mother and her baby needs to be counselled individually and IOL can be offered to those willing to achieve a vaginal birth.

Data on the safest mode of delivery for fetuses affected with various birth defects and their mothers is ambiguous (Kuller et al., 1996). Generally, potential fetal benefits of avoiding birth trauma and stress should be carefully weighed against the maternal risks of surgery which should not be underestimated. Vaginal delivery, spontaneous or following IOL can be attempted in the majority of patients (Wataganara et al., 2017). There are certain conditions, when scheduled operative delivery is indicated, such as meningomyelocele, hydrocephalus complicated by macrocephaly, abdominal wall defects with liver herniation, sacrococcygeal teratoma (Kuller et al., 1996) or those requiring ex utero intrapartum treatment, for example fetal neck tumours, but these are rare.

1.4.6 Fetal growth restriction

Fetal growth restriction (FGR) affects 1 in 10 pregnancies and has a potential to adversely affect perinatal outcomes (Frøen et al., 2004). It is defined as a failure to reach the fetus's own growth potential in utero due to environmental, placental, or genetic factors. Intrauterine growth restriction carries a substantial risk of perinatal morbidity and mortality. This not only includes short term consequences such as

iatrogenic or spontaneous preterm birth and hypoxia but also, long term neurological or cognitive impairment, cardiovascular and endocrine disease, as well as stillbirth or neonatal death. The diagnosis of FGR is usually made by a comparison of fetal size to the reference population and the estimated fetal weight below the 10^{th} centile is used. This arbitrary cut off makes it difficult to distinguish the constitutionally small babies whose risks are substantially smaller, from those deprived of nutrition. (Nardozza et al., 2017).

In view of the risks listed above associated with FGR, its detection and management is crucial. It reduces the risk of stillbirth 20 times when compared to undetected smallness (Selvaratnam et al., 2020). Adequate screening, prevention, surveillance, and timely delivery of fetuses at risk and those affected by intrauterine growth restriction has been made one of the pillars of the Saving Babies Lives Care Bundle used in the UK to reduce the stillbirth rate. Therefore, various organizations and professional bodies such as NICE, RCOG and ACOG developed their own guidelines to implement efficient and effective ways to deliver antenatal care.

The Royal College of Obstetricians and Gynaecologists developed a screening pathway based on risk factors identification and a stepwise follow up depending on an overall risk score (Green-top Guideline No. 31). Severe early onset fetal growth restriction often leads to iatrogenic preterm delivery usually by caesarean section. RCOG recommends an operative delivery of small for gestational age (SGA) fetuses with absent or reversed end diastolic flow during their ultrasonographic Doppler

assessment. However, late onset FGR can be managed conservatively with frequent monitoring of fetal growth and well-being.

In these pregnancies planned IOL at term is not unreasonable even in cases with an unripe cervix. The risk of caesarean section in these cases depends on maternal age, obstetric history, and fetal umbilical artery Doppler prior to IOL. Overall neonatal outcomes seem to be comparable in women who delivered vaginally and those who underwent caesarean section. An elective operative delivery does not appear to protect against poor neonatal outcomes in these babies (Pinton et al., 2020).

Interestingly, in pregnancies when intrauterine growth restriction is suspected in the late third trimester (between 36 and 41 weeks) with absence of any other risk factors, IOL and expectant management with vigorous fetal and maternal monitoring, seem to result in similar outcomes (Boers et al., 2010; Hidaka et al., 2018). Additionally, women who decide to undergo an IOL in these circumstances, can be reassured that it does not appear to increase their risk of assisted vaginal or operative delivery (Boers et al., 2010; Kehl et al., 2019). This study, however, was underpowered to determine if conservative management increases the risk of late fetal demise which should always be discussed with the parents (Boers et al., 2010).

Small for gestational age (SGA)	Timing of birth
SGA with normal Doppler studies	Initiate delivery at 37 weeks
SGA with low PI in MCA	Initiate delivery < 37 weeks
SGA with raised PI in UA	Initiate delivery at 37 weeks
SGA with raised PI in UA and static growth	Initiate delivery ≥ 34 weeks
SGA with abnormal DV	Initiate delivery < 32 weeks

Table 1.4 Timing of birth in women with SGA. RCOG Greet Top Guideline No 31

Small for gestational age fetuses seem to have less placental reserves to undergo the stress of labour. Therefore, it is reasonable to consider the most adequate and the safest method of IOL in these cases. Currently, large systematic review and meta-analysis was undertaken to establish the most suitable induction agent. It concluded, that mechanical methods using a Cook balloon or a Foley catheter carry the least adverse intrapartum outcomes such as uterine tachysystole or caesarean section for fetal distress when compared to misoprostol or dinoprostone (Familiari et al., 2020; Villalain et al., 2019). The quality of included studies, however, was described as low due to significant heterogenicity (Familiari et al., 2020). On the other hand, vaginal dinoprostone used for IOL in women with pregnancies complicated by late onset FGR with normal fetal monitoring appears to be equally safe when compared to its use in normal pregnancies. The rate of caesarean sections or immediate fetal outcomes seem to be similar (Ben-Haroush et al., 2004). Each delivery suite in the country developed

its own policy with regards to the IOL process for these women. Most, if not all of them, offer continuous fetal monitoring to ensure safe process.

In view of the significant cost burden related to IOL for fetal growth restriction, the study was conducted to establish the most cost effective and safe method of IOL. It showed that the use of misoprostol was significantly cheaper when compared to dinoprostone or a Cook balloon with similar maternal and neonatal outcomes (Duro-Gómez et al., 2017a, 2017b). However, this method of IOL has not been adopted by obstetricians in the UK.

An interesting point has been raised by a group from Barcelona, who incorporated the cerebroplacental ratio into their prediction model for operative delivery in women induced for FGR (Garcia-Simon et al., 2015). This uptake seems to be more accurate in predicting the risk of emergency caesarean section, but it requires an ultrasonographic assessment of the middle cerebral artery and umbilical artery Doppler 24 hours prior to IOL.

1.4.7 Large for gestational age

Fetal macrosomia is a term used to describe a large fetus. Antenatally, it is defined as an estimated fetal weight (EFW) above 4000g regardless of gestational age. It can also be used postnatally to describe new-borns more than 4000g at birth. Overall, it complicates about 10% of pregnancies worldwide (Magro-Malosso et al., 2017)

(Araujo Júnior et al., 2017). Authors of different studies choose different cut-offs to define fetal macrosomia and the lack of universal definition causes confusion, and it is likely responsible for over or underreporting. Ye et al. came up with an interesting approach to define macrosomia based on fetal outcomes such as stillbirth, a low Apgar score at the 5th minute of life and neonatal death in four birthweight subgroups between 4000g and 4999g. They noticed that fetal mortality and morbidity does not increase in fetuses smaller than the 97th centile across the entire study population, regardless of patients' ethnic origin. However, odds ratios for adverse neonatal outcomes were significantly higher when estimated fetal weight exceeded 4500g for patients of White ethnic origin and 4300g in African-Caribbean and Hispanic populations (Ye et al., 2014). Many obstetricians and researchers use the term large for gestational age to describe big babies regardless of gestation and different cut-offs of 90th, 95th or 97th centile are used depending on the centre.

In utero fetal size assessment can be performed with abdominal palpation, by measuring symphysis fundal hight (Niswander et al., 1970) (Beazley & Underhill, 1970) or performing an ultrasound to estimate fetal weight (Mgbafulu et al., 2019). A variety of formulas have been researched to ensure that the most accurate estimation is being used. Despite extensive research, it seems like, the formula developed in 1985 by Hadlock et al. based on head circumference (HC), abdominal circumference (AC) and femur length (FL) is still the most accurate one. The association between EFW and birth weight is linear and within a 10% range in the vast majority of cases (80%) (Goto, 2020; Hammami et al., 2018). Out of the three methods listed above, the

ultrasound estimated fetal weight seems to be the most reliable in assessing fetal size and it should be used in developed countries. Clinical assessment should be reserved for the low risk population or for assessment in developing countries where access to ultrasound techniques is limited (Joshi et al., 2017).

Fetal macrosomia is often a result of poorly controlled diabetes mellitus, including type 1, type 2 and gestational diabetes (Kc et al., 2015). It is also more common in obese women (Dai et al., 2018). In one in ten pregnancies, however, it occurs as an independent complication and may be associated with adverse maternal and neonatal outcomes such as prolonged labour, failure to progress in the first or second stage of labour, instrumental delivery, caesarean section, perineal trauma including 3rd and 4th degree tears, shoulder dystocia with possible brachial plexus injury or fetal bone fractures as well as postpartum haemorrhage (Magro-Malosso et al., 2017; Ye et al., 2014). In order to avoid possible complications, IOL for mothers carrying large for gestational age fetuses seems reasonable. Notwithstanding, the data supporting labour induction for pregnancies affected by macrosomia is not as extensive as for example for fetal growth restriction. A systematic review and meta-analysis demonstrates that there is no difference in caesarean section and instrumental delivery rates, birth asphyxia or shoulder dystocia between IOL and expectant management groups. The incidence of fetal fractures seems to be significantly lower in women who are offered an IOL at 38 weeks gestation or later. The time to delivery and mean fetal birthweight (BW), including the rates of BW exceeding 4000g and 4500g is lower in inducted

women when compared to those who await spontaneous onset of labour (Magro-Malosso et al., 2017).

The Cochrane review supports the results of the above meta-analysis and advocates leaving the choice to women. To avoid one fetal fraction, sixty labour inductions need to be performed. However, taking into consideration, that the process does not seem to have significant disadvantages, many women choose this option to shorten their pregnancy (Boulvain et al., 2016). Most obstetricians would agree that birthing a large baby is a common fear of pregnant women.

There is no consensus on the best timing for IOL in these patients. The Royal College of Obstetricians and Gynaecologists does not support IOL if the reason for the intervention is solely suspected fetal macrosomia. However, most obstetricians in the UK would schedule an IOL between 39- and 40-weeks' gestation at the request of a woman who carries a large fetus. Additionally, most professional bodies, including RCOG supports IOL for obese or diabetic women with LGA fetuses.

1.4.8 Maternal request

Pregnancy is a stressful time for most women. It imposes complex somatic and psychological changes. Nulliparous women are at particular risk of experiencing the pregnancy as a powerful psychological event. Apart from obvious physiological changes, most women experience fear and report concerns with regards to the outcome

of the pregnancy. This makes them particularly vulnerable and therefore, robust social and partner support is required. Pregnancy and the transition to parenthood puts a strain in most relationships which makes the situation complex and multifactorial (Bjelica et al., 2018; Bjelica & Kapor-Stanulović, 2004). Women often feel they lose control over their body and most decisions are made in their best interest. Providing good quality, evidence-based information in a timely manner helps women take ownership and make informed choices. Most patients want to be involved in decision making process with regards to their body, pregnancy, and delivery of their baby. It improves women's experience and positively impacts their mental health (Coates et al., 2019).

Many countries worldwide, including the UK, allow women to request an elective caesarean section as their preferred mode of delivery despite contraindications to vaginal birth. The main reasons why women would opt for this option seems to be a fear of pain during labour, prolonged labour, lack of support, loss of control, time of birth and anxiety related to birth trauma including fetal injury as well as perineal tears (Jenabi et al., 2020). Most of these reasons are not specific and could be tackled during a consultation involving a medical professional and a patient. In the UK, the role of mode of delivery counsellors has been successfully taken over by specialist consultant midwives, who are able to help women plan their labour taking into consideration their wishes.

WHO, in its recommendations for intrapartum care for a positive childbirth experience, from a 2018 meeting in Geneva, emphasises the importance of involving women in the decision making process. There is a growing body of evidence supporting shared decision making which is likely to improve outcomes and healthcare experience (Elwyn et al., 2012; Hauser et al., 2015; Stacey et al., 2017). It seems like, an IOL, could potentially help women gain control over the time and place of birth. It is likely to be less invasive than caesarean section and because it is usually performed on delivery suits, and pain relief such as an epidural analgesia could be easily facilitated. It is surprising that in this context, an IOL for maternal request is still not offered to women who express their concerns around the time and the mode of delivery.

NICE guideline on IOL does not recommend this procedure solely on maternal request without any obstetric indication. Some experts believe, however, that the option of labour induction at term should be available to women and call for more studies examining women's views (Norman & Stock, 2016).

Despite the lack of recommendations from professional bodies, IOL is often considered for women who experience moderate to severe anxiety in the antenatal period. This might be related to fears around fetal well-being as a consequence of previous pregnancy loss or a poor obstetric outcome (Coulm et al., 2016). Women sometimes experience a deterioration in their mental health status when passing the

point in their pregnancy when they feel increasingly uncomfortable in their bodies or when they have lost a previous pregnancy in an unexplained situation.

Another small but significant group of patients who are likely to enquire about an IOL are multiparous women who wish to pragmatically plan their birth in a timely fashion to facilitate family life organisation. The risk of induction failure in these women is significantly lower. Therefore, obstetricians are more likely to accept their request. The fear of precipitate labour and a possibility of birth outside of medical settings is a reasonable indication for an elective IOL (Coulm et al., 2016).

Interestingly, private healthcare institutions are more likely to agree to women's request of scheduling an IOL despite the lack of any medical indications. It is possible, that private obstetricians are more sensitive to women's wishes and their feelings. It also seems easier to manage the workload when deliveries are planned (Coulm et al., 2016; Fisher et al., 1995).

1.4.9 Advanced maternal age

Some authors define advanced maternal age as pregnancy at the age of 35 and above (L. Dunn et al., 2017; Figuerêdo et al., 2014; Kwayke-Ackah et al., 2020; Ojule et al., 2011; Walker et al., 2016; Wang et al., 2011). However, in a modern world, where women wish to pursue a successful career and achieve financial stability before they embark on pregnancy and start their family, we see an increasing number of women

who postpone childbearing beyond the age of 35 or even 40. On the other hand, in developing countries where there is a culture and tradition of supporting a large family size, we see multiparous older women. Therefore, especially in high-income countries including the UK, the cut-off of 40 years of age is used to capture pregnancies at higher risk of complication related to advancing maternal age (Bergholt et al., 2020; Ngowa et al., 2013).

The Office of National Statistics in England and Wales reports a steadily increasing childbearing age over the last 40 years. It was 26.4 in 1975 and 30 in 2013. The number of women delivering in their 30s and 40s is rising gradually (Fitzpatrick et al., 2017). In 2006, 20% of all births were attributed to women aged 35 or older.

The rate of obstetric interventions is higher amongst older women, and they typically classify themselves as a high risk pregnancy group. On average, one in four pregnant women in the UK requires delivery by caesarean section. Operative delivery rate in nulliparous women older than 35 reaches 38% and is as high as 50% in women older than 40 (Walker et al., 2016). There seems to be a linear relationship between the age and rate of emergency caesarean sections in women who expect their first baby. Although the biological bias could not be excluded (Smith et al., 2008).

Advancing maternal age is associated with the increased possibility of adverse maternal and neonatal outcomes. The risk of gestational diabetes, fetal macrosomia, hypertensive disorders, preterm delivery, and placental disorders such as placenta

praevia, placental abruption or fetal growth restriction as well as perinatal death is greater in these women (Figure 1.11). Fortunately, the absolute rate of the above complications is low (Joseph et al., 2005; Pinheiro et al., 2019; Walker et al., 2016).

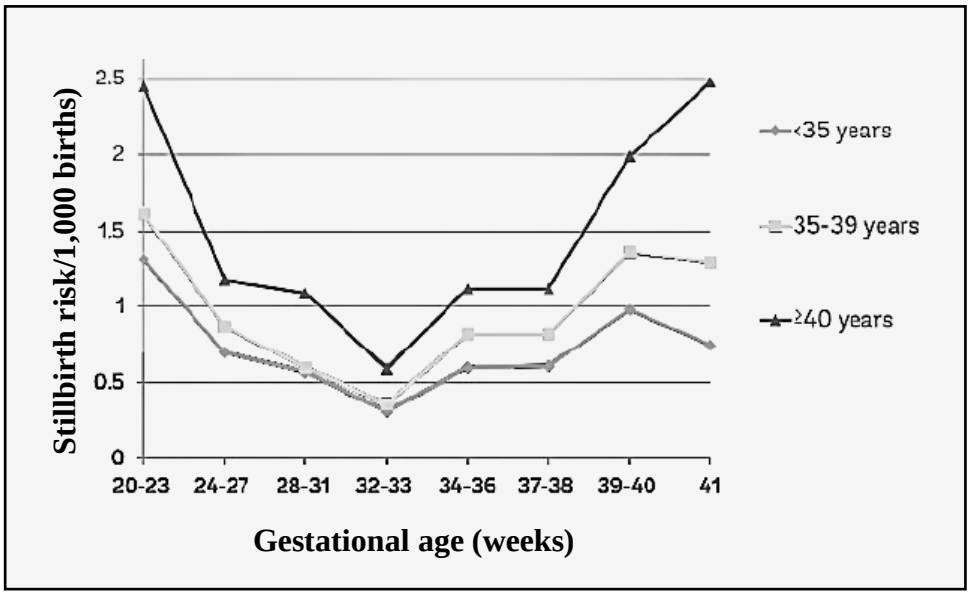


Figure 1.11 Relationship between gestational age and the risk of stillbirth in women > 35 years old in the USA in 2001-2002. (Reddy et al., 2006)

Because there is a small age-related increased risk of stillbirth at term, it makes sense to undertake a pragmatic approach of inducing labour as soon as the benefits outweigh the risks. The greatest rise in the cumulative risk of late fetal demise in women older than 35 starts at 39 weeks and cumulates at 41 weeks gestation. There is a fine line between the dangers of continuing the pregnancy and possible complications related to iatrogenic interventions required to achieve a timely delivery. IOL itself does not seem to increase the risk of emergency caesarean section as previously thought (Crequit et al., 2019; Kwayke-Ackah et al., 2020; Walker et al., 2016). Therefore,

some experts advocate that IOL could be safely offered to women older than 35 as early as at 39 weeks gestation (Walker & Thornton, 2021).

The Royal College of Obstetricians and Gynaecologists in their Scientific Impact Paper No 43 advises IOL between 39 and 40 weeks' gestation to women older than 40 in order to prevent late stillbirth. It is estimated that women in their 40s have a similar risk of stillbirth at 39 weeks as women in their 20s at 41 weeks gestation. IOL can be considered earlier if there are any comorbidities and should be strongly advised to women especially if they are overweight, of African Caribbean ethnic origin or are in their first pregnancy. Some women may request an elective caesarean section over a labour induction. Their wish should be respected, and the risks, benefits and possible complications of both procedures should be discussed in detail and documented in patients' maternity notes.

1.4.10 Obstetric cholestasis

Obstetric cholestasis (OC) is also known as an intrahepatic cholestasis of pregnancy (ICP). It is the most common liver and bile acid disorder unique to pregnancy. Its prevalence is between 0.4% and 1% in Europe and North America but significantly higher in certain South American countries such as Bolivia and Chile, reaching as many as 1.5% to 4% of all pregnancies. Women suffering from this disease report a generalised itch, which predominantly affects their palms and soles, without any identifiable skin rush. Apart from maternal pruritus, elevated liver enzymes and/or

serum bile acids are often present. ICP usually occurs in the third trimester of pregnancy but can start as early as 7 weeks gestation in particularly high-risk patients. Both, clinical symptoms and biochemical changes, usually resolve spontaneously following delivery and these women are typically unaffected outside of pregnancy. (Pataia et al., 2017).

There are numerous physiological adaptations occurring in any normal pregnancy. One of them is a change to bile acid homeostasis and metabolism. In some women this process becomes pathological and leads to ICP (McIlvride et al., 2017). Because of the important role liver plays in pregnancy, supporting metabolic needs of the growing fetus, increasing demands may sometimes uncover an underlying hepatic susceptibility (Pataia et al., 2017).

Obstetric cholestasis, especially its severe form, is linked to adverse perinatal outcomes. It increases the risk of spontaneous or iatrogenic preterm delivery, intrapartum fetal hypoxia, admission to neonatal unit as well as the risk of stillbirth (Geenes et al., 2014). Current evidence suggests that the risk of stillbirth is significantly increased in women with severe cholestasis whose bile acids concentrations exceed 100µmol/L. This is a significantly higher level than the previously quoted 40µmol/L. To reduce the distress that the counselling about the risk of late fetal demise may cause, women diagnosed with mild ICP should be reassured and monitored closely with regular liver function tests until delivery (Ovadia et al., 2019). Additionally, women affected by ICP have a higher risk of developing other

metabolic and endocrine complications of pregnancy such as preeclampsia and gestational diabetes (Wikström Shemer et al., 2013)

Ursodeoxycholic acid (UDCA) is the most prescribed drug in patients diagnosed with ICP. It is safe and does not adversely affect the pregnancy in any way. However, its effect on the disease was recently evaluated and it seems like it does not reduce the risk of adverse perinatal outcomes and its use has been questioned (Chappell et al., 2019). There is a potential to lower the production of bile acids and to cause a positive effect on maternal pruritus (Ovadia et al., 2020). Although, this effect is possibly too small, to be clinically significant (Chappell et al., 2020).

In view of the lack of treatment for ICP and its potentially negative impact for the pregnancy, a timely, planned delivery seems to be the only clinically significant intervention available to obstetricians. Early, but term IOL at 37 weeks for patients with significantly raised bile acids (>40µmol/L) does not seem to disadvantage them in terms of mode of delivery, length of labour or neonatal outcomes. Their new-borns, however, were smaller when compared to those delivered by women in the expectant management group, which is understandable (Friberg et al., 2016). Women with mild ICP should be offered an informed discussion including the risks and benefits of IOL at 38 weeks versus expectant management. It does not seem to make any difference to this cohort. Women's choice should be taken into consideration (Nielsen & Lykke, 2021).

The Royal College of Obstetricians and Gynaecologists recommends a discussion about timing of delivery with every woman diagnosed with ICP. It should include consideration of labour induction after 37 weeks gestation. The difficulty in fetal monitoring with regards to prediction of stillbirth should be explained. The risk of fetal prematurity, respiratory distress and failed IOL resulting in operative delivery should be weighed against the potential risk of losing the pregnancy at term. Fetal death in these cases is usually sudden and it cannot be predicted neither by serial ultrasound scans nor by regular CTGs. Severity of the condition should be estimated for each patient and the plan should be made individually.

1.4.11 Polyhydramnios and oligohydramnios

Polyhydramnios

Polyhydramnios is an increased amount of amniotic fluid surrounding the fetus. Objective evaluation of liquor is difficult and it has been established that the most accurate and reproducible assessment is ultrasonographic measurement of a single deepest vertical pocket of fluid of above 8cm (Chamberlain et al., 1984). It affects 0.5% to 2% of pregnancies and it is often related to a variety of fetal and maternal conditions such as diabetes mellitus, fetal genetic or structural abnormalities, macrosomia, in utero infections or haemolytic disease. In these situations, antenatal and intrapartum management depends on the primary cause of polyhydramnios. However, in about half of the cases, the cause of excessive amniotic fluid cannot be

identified. In these situations, idiopathic polyhydramnios is diagnosed (Magann et al., 2007).

There are no clear recommendations from professional bodies on what management should be offered to women whose pregnancies are affected by idiopathic polyhydramnios. Some evidence suggests that it increases the risk of malpresentation, prolonged first stage of labour, failure to progress and caesarean section (Zeino et al., 2017). Due to its potentially negative effect on perinatal outcomes, IOL is not unreasonable and could be offered to these women. However, The Obstetrician and Gynaecologist (TOG) review article, used by practising obstetricians in the UK in situations where there are no official RCOG guidelines, reports insufficient evidence to support IOL for idiopathic polyhydramnios.

Oligohydramnios

Oligohydramnios, in contrast, is a reduced amount of amniotic fluid surrounding the fetus in utero. The most common definition is a single deepest vertical pocket (DP) of fluid of less than 2cm or amniotic fluid index (AFI) of less than 5cm (Phelan et al., 1987; Rutherford et al., 1987). Robust evidence suggests that using DP measurement is more accurate when compared to AFI. The latter, increases the rate of diagnosis of isolated oligohydramnios, the number of inductions of labour and the risk of caesarean section without any negative impact on perinatal outcomes (Marks Kazatsker et al., 2019; Nabhan & Abdelmoula, 2008).

Oligohydramnios can be related to the spontaneous rupture of membranes, fetal growth restriction, fetal birth defects such as renal agenesis or chromosomal abnormalities. Isolated oligohydramnios, when none of the above is found to be the cause of reduced liquor, affects between 0.5% and 5% of pregnancies

In pregnancies complicated by isolated oligohydramnios at term, most clinicians would offer an active management with IOL to avoid possible perinatal complications resulting from placental insufficiency, meconium staining or umbilical cord compression (Schwartz et al., 2009; Shrem et al., 2016). Women induced at term for isolated oligohydramnios seem to have comparable maternal and neonatal outcomes to women induced for oligohydramnios as a result of other complications (Tahmina et al., 2020). IOL offered to women with reduced liquor volume seems to result in a lower caesarean section rate and overall better perinatal outcomes when compared to conservative management and awaiting spontaneous events.

Neither Royal College of Obstetricians and Gynaecologists nor National Institute for Health and Care Excellence specifically recommends an IOL for isolated oligohydramnios at term. However, when diagnosed by an opportunistic ultrasound scan, most clinicians take an active approach and offer intervention. In the UK, scans at term are not commonly performed. There is usually another reason to assess fetal well-being by ultrasound, such as reduced fetal movements. Therefore, an incidental finding of oligohydramnios in these cases is difficult to ignore.

1.4.12 Post-dates pregnancy

The World Health Organisation (WHO 1996) defines full term pregnancy as pregnancy from 37 until 42 weeks gestation. The prevalence of postmaturity varies between countries. In the USA it is between 1% and 2.5%. In Europe, the rate of postdates births ranges from 0.4% in Austria to 7% in Denmark and Sweden. The general approach to prolonged pregnancy is either a universal IOL around 42 weeks gestation or a close monitoring of pregnancies which extend beyond 41 weeks and selective intervention in cases of any abnormality. The number of macrosomic infants who weighed above 4500g at birth was significantly higher in countries where expectant management was a norm (Zeitlin et al., 2007).

Epidemiological analysis showed that perinatal outcomes are worse in cases of postmaturity when compared to pregnancies which end at 40 weeks gestation. Rates of neonatal morbidity and mortality seem to be significantly higher in overdue pregnancies. Reasons, why some women go into labour around their due date, and some go overdue are poorly understood. There is some evidence that diet, pharmacological treatment and environmental factors could play a role (Shea et al., 1998). In view of the above findings, accurate dating of pregnancy and adequate management of postmaturity is crucial.

Active management with IOL between 41- and 42-weeks' gestation is a common practice in the UK. It is justified by an increasing risk of pregnancy loss with advancing

gestation. The rate of stillbirth at 37 weeks is 0.35 per 1000 pregnancies and it increases six times at 43 weeks gestation, reaching 2.2 stillbirths per 1000 pregnancies (Budden et al., 2014). The mortality rate for children up to 12 months falls steadily until 41 weeks gestation. It then plateaus and increases significantly in postmature pregnancies. Two points listed above explain why IOL beyond 41 weeks gestation should be offered routinely to every women (Middleton et al., 2018). Risks of losing a pregnancy significantly override the benefits of awaiting spontaneous events (Walker & Thornton, 2021). Especially, after several important research studies proved that an elective IOL as early as 39 weeks, does not impact perinatal outcomes negatively. Additionally, it does not affect the rate of emergency caesarean sections and possibly can even lower it (Grobman et al., 2018; Saccone et al., 2019).

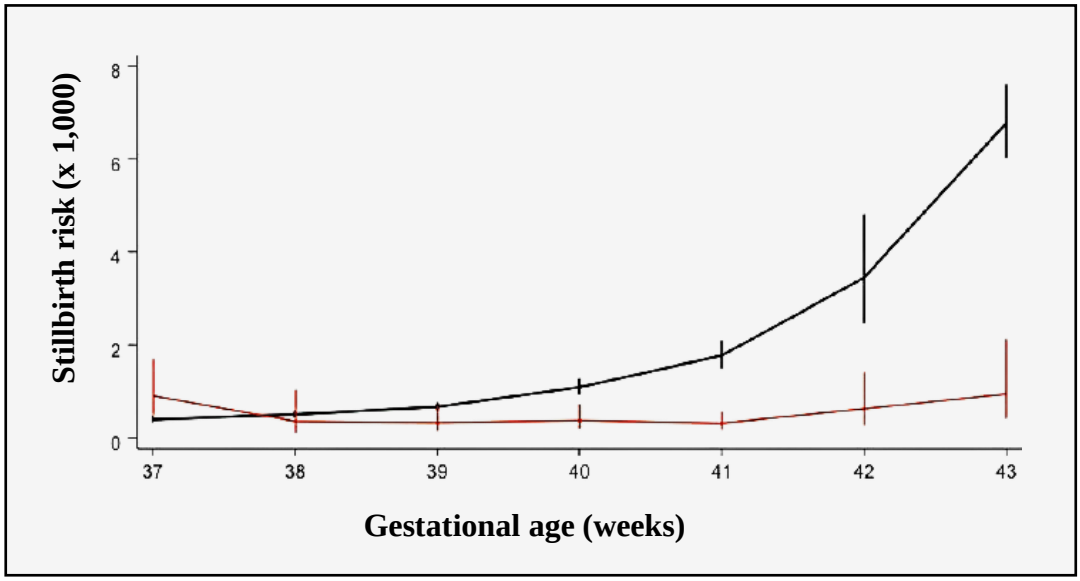


Figure 1.12 Prospective risk of stillbirth per 1,000 pregnancies and risk of neonatal death per 1,000 deliveries by gestational age in pregnancies continued to term. Stillbirth risk (solid back line); neonatal death risk (solid red line). (Reprinted by permission from PLOS Medicine) (Muglu et al., 2019)

American data suggests that 1675 inductions of labour at 39 weeks is needed to prevent one stillbirth. The number seems high, but when we take into consideration devastating emotional consequences for grieving families, it could be worth it. An elective IOL at 39 weeks offered to a low risk population has a potential of saving 883 fetuses a year in the USA (Po' et al., 2020). The policy of an early IOL in order to prevent stillbirths has not been implemented yet, but it definitely sparks a debate on vigilant monitoring and management of pregnancies approaching the estimated due date and definitely the ones going beyond it.

1.4.13 Spontaneous rupture of membranes

Spontaneous rupture of membranes (SRM) or amniorrhexis is defined as amniotic sac rupture and drainage of amniotic fluid surrounding the fetus. Overall, the risk of SRM throughout the pregnancy is between 2% and 3%. However, it is known to be a predominant cause of preterm birth and leads up to 40% of deliveries prior to 37 weeks gestation (Morris et al., 2016). We know, that approximately 50% of women will go into spontaneous labour following membrane rupture, reaching delivery within 33 hours (Krispin, 2017).

The sequence of events leading to membrane rupture; loss of elasticity, chorion and amnion separation, chorion fracture and amnion herniation precedes the rupture of amnion. This subsequently results in amniotic fluid leakage. Possibly, the analysis of the weak point within the membrane at the level of internal cervical os, could help to

predict the rupture. This would be of an important value, especially in extremely premature pregnancies, but it is complicated and requires further research (Méhats et al., 2011).

Because prolonged amniotic fluid drainage increases the risk of infection (Yasmina & Barakat, 2017), extensive research has been done to establish the best management plan for these women. The earlier in pregnancy SRM occurs, the more complicated the situation. Risk of prematurity versus risk of infection should be considered. Most professional bodies, including the Royal College of Obstetricians and Gynaecologists, advises conservative management with oral antibiotics and close monitoring if membranes rupture before 34 weeks gestation. If a woman develops a systemic infection, immediate delivery is recommended usually by caesarean section.

Once a woman reaches gestation between 34 to 37 weeks, the risk of prematurity for the fetus is smaller. Until recently, most American and British obstetricians, following their professional body advice, would recommend an IOL to women with SRM close to term. However, following the publication of PPROMPT Trial, the recommendations have changed. Morris et al. provided good evidence, that expectant management not only reduces neonatal morbidity, but also does not seem to increase the risk of chorioamnionitis leading to a perinatal infection (Blanchon et al., 2013; Morris et al., 2016). In 2019, the Royal College of Obstetricians and Gynaecologists updated their Green Top Guideline No 73 and recommends expectant management with close maternal and fetal monitoring to all women with SRM prior to 37 weeks gestation,

unless there is evidence of Group B Streptococcus colonisation. When SRM occurs at term, delivery should be expedited and planned. Women offered augmentation of labour with intravenous oxytocin following SRM, seem to have a significantly lower infection rate and higher satisfaction level when compared to those awaiting spontaneous events (Hannah et al., 1996). It is important that IOL is offered to these women. However, the optimal interval from membranes rupture to intervention has not been specified (Zelli et al., 2013). We know, that 24 hours appears to be a safe timeframe for most otherwise healthy pregnancies and the risk of chorioamnionitis remains low. It gives women a chance to achieve spontaneous vaginal delivery without compromising their safety (Conway et al., 1984). Women are prewarned to look for signs of infection and to self-refer to a healthcare provider if they feel unwell or if the colour or the smell of the liquor changes.

The evidence supporting an immediate intervention for SRM at term when compared to labour induction within 24h was deemed to be low (Middleton et al., 2017). The Royal College of Obstetricians and Gynaecologists recommends an IOL to all women who rupture their membranes at term. The procedure can be started imminently or delayed by 24h depending on the patient's wishes.

1.4.14 Reduced fetal movements

Reduction in fetal movements is difficult to quantify as there is no formal definition as such. It is a woman's perception of how her baby moves in utero. It may reflect, a

number of movements a woman feels each day or a pattern she is used to with her baby. It is one of the most common reasons why women self-refer to maternity assessment units all over the world and it represents approximately 6% of their workload. It is estimated that 15% of pregnant women report reduced fetal movements (RFM) during their third trimester (Sergent et al., 2005) and some of them will subsequently be diagnosed with a stillbirth (Efkarpidis et al., 2004). Therefore, it is an important symptom and could be related to adverse perinatal outcomes (McCarthy et al., 2016). The difficulty arises from the lack of high-quality evidence leading to incoherent management strategies, hospital policies and even information given to the patients (Winje et al., 2016).

Fetal movements are a good sign of fetal activity and well-being. They reflect normal neuromuscular development and integrity of the central nervous system. Women start feeling their baby move, usually from 18 to 20 weeks gestation (Rayburn, 1990). Understandably, reduced fetal movements are often a cause of maternal anxiety.

Several factors may affect women's perception of fetal movements, such as anterior placenta before 28 weeks gestation, various drugs, for example antenatal corticosteroids or magnesium sulphate as well as fetal position. In the latter case, women find it difficult to perceive fetal movements, when the baby's spine lies anteriorly and both legs and arms are located towards the maternal spine. The number of movements decreases gradually in the late third trimester of pregnancy due to increasing fetal size and a reduction in the amount of liquor surrounding the fetus

(Rayburn, 1990). There are three types of movements assessed during an ultrasound scan: fetal breathing, limbs' movements and gross body movements. The latter are the most frequently reported by the mother. Movements are felt better when a woman lies down and in the evenings which is likely related to maternal diurnal activity (Cito et al., 2005).

Investigations which could help with the prediction of poor neonatal outcomes are CTG assessment, estimated fetal weight and liquor volume obtained during an ultrasound scan (Daly et al., 2011; Tveit et al., 2009). Women who self-refer with RFM and are found to have a pathological or persistently suspicious CTG are likely to be delivered by an emergency caesarean section and those found to have a pregnancy complicated by a fetal growth restriction are booked for close well-being monitoring and managed accordingly to the guidance for FGR. There is a trending perception, that risk factor identification as well as raising patients and clinicians awareness about the importance of RFM may decrease the number of adverse outcomes including stillbirths (Carroll et al., 2019). However, AFFIRM study, which was a large randomised controlled trial (RCT) and the only study which included stillbirths as a primary outcome, failed to prove that a rising awareness approach together with an improved care package to women presenting with RFM, could save babies from dying in utero (Norman et al., 2018).

The Royal College of Obstetricians and Gynaecologists recommends women to lie down and count the movements when they first have a concern. Only if they don't feel 10 movements within that time, are they advised to contact their midwife. However,

most maternal assessment units in the country would invite a woman to attend for a CTG and review straightaway. Often, the ultrasound scan is also arranged with a repeated episode of RFM. The vast majority of women (70%) who report a single episode of RFM have an uncomplicated pregnancy and a good neonatal outcome. Women reporting a recurrent reduction in fetal movements seem to be at higher risk of complications (Sinha et al., 2007). In view of the lack of high-quality evidence regarding intervention in these patients, careful discussion should take place between a senior obstetrician and a patient. Often IOL is arranged for women repeatedly reporting RFM at term, even in the presence of normal fetal growth, liquor and Doppler studies on the ultrasound scan.

1.4.15 In vitro fertilization

In vitro fertilization (IVF) has become a routine management for the treatment of infertility in developed countries. In the UK, approximately 1% of births is attributed to this technique (RCOG Scientific Impact Paper No. 8).

The effects of assisted reproductive technology (ART) on perinatal outcomes have been studied for number of years. Worse pregnancy outcomes following IVF, when compared to spontaneous conception were attributed to a high rate of multiple pregnancies resulting from ART. However, even since the importance of single embryo transfers have been highlighted and policies regulating multiple pregnancy rates following ART have been implemented, the statistics have not shifted

significantly and still IVF pregnancies carry a higher risk of antenatal complications (Pandey et al., 2012).

Pregnancies resulting from ART are at higher risk of complications such as antepartum haemorrhage (RR 2.49), congenital anomalies (RR 1.67), hypertensive disorders (RR 1.49), premature, prelabour rupture of membranes (RR 1.16), delivery by CS (RR 1.56), birthweight of less than 2500g (1.65), birthweight of less than 1500g (1.93), delivery before 37 weeks (RR 1.54), delivery before 32 weeks (RR 1.68), gestational diabetes (RR 1.48), admission to Neonatal Intensive Care Unit (NICU) (RR 1.58) and finally perinatal mortality (RR 1.87) (Pandey et al., 2012). Women undergoing IVF treatment are also susceptible to bleeding in early pregnancy (OR 4.59) and ovarian torsion (OR 10.9). It appears that standard IVF increases these risks more significantly than intra-cytoplasmatic sperm injection (ICSI) (Källén et al., 2005).

It is, therefore, surprising that NICE does not recognise singleton IVF pregnancies as high risk. RCOG, in their Scientific Paper No 8 mentioned above, acknowledges higher antenatal risk for these women and recommends an appropriate risk stratification. Once a woman goes into labour, the outcomes seem to be comparable for IVF pregnancies and those following a spontaneous conception (Verlaenen et al., 1995).

IOL seems significantly more likely in women who underwent IVF (Jenabi & Khazaei, 2018). This is often related to more advanced maternal age, pre-existing medical

conditions or complications arising during pregnancy. However, many obstetricians in the UK would offer an IOL around the due date, to women who underwent IVF treatment solely to minimalize the risk of complications and to reduce maternal anxiety.

1.4.16 Contraindications for induction of labour

Contraindications for IOL are basically the same as contraindications for vaginal delivery. They can be divided into maternal and fetal contraindications. There are few absolute contraindications to IOL, such as placenta praevia, morbidly adherent placenta and vasa praevia. In the above conditions, uterine contractions leading to cervical dilatation may cause a major haemorrhage. Cord prolapse is an emergency where the fetus is at significant risk of hypoxia and birth asphyxia. Delivery should be by an emergency caesarean section unless vaginal delivery is imminent. Similarly, cases of acute fetal distress resulting from placental abruption should be delivered operatively. Transverse fetal lie (sideways in the uterus), some maternal or fetal abnormalities and birth defects are incompatible with vaginal delivery. Women who had a major uterine surgery with classical incision (midline incision) are advised against vaginal delivery due to the risk of scar rupture as high as 10%. Certain maternal infections including HIV with a high viral load or active genital herpes with first presentation in 3rd trimester of pregnancy, carry significant risk of transmission to the new-born during vaginal delivery and therefore IOL is contraindicated.

Relative contraindications to IOL and vaginal delivery are multiple pregnancies with more than two fetuses, breech presentation in nulliparous woman and repeated lower segment caesarean sections. Most women and clinicians would choose an elective caesarean section in these situations. However, if the patient is determined to try and achieve vaginal delivery, the IOL could potentially be considered after detailed discussion between a woman and a senior obstetrician, including all possible risks and complications. (RCOG eLearning module on Induction of labour)

1.5 Pre-induction cervical assessment

The uterine cervix should be examined prior to undertaking IOL. It is important to establish the state of cervical ripening in order to adequately assess the preparation for a vaginal delivery (NICE CG 70). The examination should be performed by a trained medical professional who will be able to objectively describe physiological changes to the cervix.

1.5.1 Bishop score

Edward Bishop in 1964 addressed the importance of several maternal and fetal factors prior to selecting women for an elective IOL (Bishop, 1964). These include fetal presentation, gestational age as well as maternal obstetric history, parity and most importantly consent for the procedure (Wormer et al., 2020). He also established an objective pelvic scoring system which is used all over the world by midwives and

obstetricians. This system is known as the Bishop score and takes into consideration: cervical dilatation, consistency, effacement/cervical length and position as well as a station of presenting fetal part in relation to maternal ischial spines (Laughon et al., 2011; Wormer et al., 2020).

Score	0	1	2	3
Dilatation	Closed	1-2 cm	3-4 cm	5 cm
Consistency	Firm	Medium	Soft	-
Length	>4 cm	3-4 cm	1-2 cm	0/fully effaced
Position	Posterior	Midline	Anterior	-
Station	-3	-2	-1/at spines	+1/+2

Table 1.5 Bishop scoring system.

Bishop score ranges from 0 to 13 and a score of 8 or more is considered a favourable or ripe cervix (NICE CG 70). The higher the score, the greater the chance for spontaneous onset of labour. If we compare the cut off of BS 4 (OR = 1.98; 95% CI: 1.58-2.48) to BS 8 (OR = 5.48, 95% CI: 1.67-17.96) there is a clear association of higher Bishop score with achieving a successful vaginal delivery regardless of the time interval between intervention and delivery (Teixeira et al., 2012). Additionally, there is a positive correlation between the Bishop score and entering the active stage of labour as well as successful vaginal delivery per each unit increase on the scoring system (Teixeira et al., 2012).

All the above components (Table 1.5) are assessed at the same time during vaginal examination. Cervical dilatation is measured in centimetres. It is an estimated diameter of the open cervix from 1 to 10 cm. Consistency refers to how the cervix feels during the examination. Pre-labouring cervix is firm, and the consistency is similar to the tip of the nose. The more ripe the cervix, the softer it becomes. The feel of the soft cervix is similar to the softness of lips. The length of the cervix, also known as an effacement, is a measurement from the fetal head at the level of the internal os to the external os of the cervix (Wormer et al., 2020). A pre-labouring cervix measures between 2 and 4 cm in most women with an average of 38mm at 20 weeks gestation (Jafari-Dehkordi et al., 2015). This measurement shortens closer to the onset of contractions. Effacement is a shortening of the cervix, and it is expressed in percentages. Full length of the cervix is considered to be 0% effaced and a paper thin cervix in established labour is 100% effaced (Hutchison et al., 2020; Wormer et al., 2020). Position is described as a tilt of the cervix towards sacral bone (posterior), in line with a pelvic outlet (midline) and tilted towards symphysis pubic (anterior). Assessment of the station requires the assessor to identify maternal ischial spines during vaginal examination and establish how many centimetres above (-) or below (+) the ischial spines, the presenting fetal part is. Some components of the Bishop score corelate with prediction of successful IOL more than others (Teixeira et al., 2012). Dilatation of cervix and fetal head station in the birth canal seem to be more discriminative than cervical length/effacement, consistency and position (Lange et al., 1982; Lyndrup et al., 1992; Watson et al., 1996). Therefore, the same value of Bishop score could have

a different impact on the outcome of IOL, depending on the individual components which contributed to the overall score (Teixeira et al., 2012).

Bishop score is the most commonly used method of cervical ripening assessment. It is cheap, does not require any specialist equipment and is relatively easy to learn (Peregrine et al., 2006). The basis of Bishop score and vaginal examination is digital palpation and its interpretation by every assessor, which makes it subjective with significantly high inter and intra-observer variation (Faltin-Traub et al., 2004; Jackson et al., 1992; Peregrine et al., 2006). Cervical assessment performed by two equally trained medical professionals will result in the same Bishop score only in one third of examined women. If we are prepared to accept one unit difference between the assessors then agreement rises to two thirds (Faltin-Traub et al., 2004). Overall, Bishop score can be used in prediction of successful vaginal delivery with sensitivity as high as 75% and positive predictive value of 83%. However, the specificity and the negative predictive value is known to be poor (Wormer et al., 2020).

1.5.2 Cervical length

The measurement of cervical length is predominantly used in prediction of preterm delivery (Andersen et al., 1990; Sonek & Shellhaas, 1998). In many countries this ultrasonographic measurement combined with clinical examination is a standard procedure to establish the likelihood of premature delivery in patients with singleton

pregnancies and a history of previous preterm birth or other risk factors (McIntosh et al., 2016; Ville & Rozenberg, 2018).

Recently, many researchers compared transvaginal sonography for cervical measurement with traditionally used Bishop score in order to make a cervical assessment more objective. Some of them incorporated cervical length into their models of prediction of successful labour induction (Kehila et al., 2016; Kehila et al., 2015; Pandis et al., 2001; Uyar et al., 2009). This technique requires more training than digital vaginal examination and additional experience in transvaginal ultrasonography.

Transvaginal measurement of the cervix should be performed with an empty bladder to avoid false elongation of the cervix (Sonek & Shellhaas, 1998). The transducer should be placed in the vagina and care should be taken to avoid the distortion of cervical position or shape. The cervical length is measured in a longitudinal view. Side to side gentle movements might need to be applied to identify the cervix as often it does not lie within maternal sagittal axis. Applied pressure should be minimal to ensure accurate measurement. The callipers should be placed at the level of internal and external os and the distance between these points, is the cervical length. Three measurements should be obtained, and the best image selected. If images are of an adequate quality, the shortest measurement should be used (Pandis et al., 2001; Sonek & Shellhaas, 1998; Sonek et al., 1990). On average, vaginal sonography for cervical length assessment lasts about 5 minutes. It is better tolerated by women then digital

vaginal examination (Paterson-Brown et al., 1991). Additionally, it was found to be significantly less painful on the Visual Analogue Scale (Tan et al., 2007).

There is a discrepancy within the results of studies evaluating the relationship between cervical length and onset of labour or success of labour induction resulting in vaginal delivery. This might be related to a variety of definitions of what successful IOL means and how quickly following IOL a woman should deliver (Kehila et al., 2016). Moreover, cervical ripening is a dynamic process which occurs in the third trimester of pregnancy. Therefore, ultrasonographic assessment of cervical length should be interpreted according to gestational age (Rozenberg et al., 2005). In comparison to Bishop score, cervical length lacks assessment of fetal station and cervical consistency which seems to corelate with IOL outcomes (Lange et al., 1982). Generally, the longer the cervix, the lower the chance for successful vaginal delivery. The likelihood of failed IOL leading to an emergency Caesarean section increases by 10% with every millimetre in cervical length above 20mm (Rane et al., 2004). Overall, the cervical length measurement during transvaginal ultrasound scan seems to be a better predictor of labour induction outcome than the vaginal assessment of cervical length or Bishop score (Rane et al., 2003). In addition, maternal history of previous vaginal birth is an independent factor for successful IOL. In parous women the interval from induction to delivery was 37% lower than in nulliparous women despite an identical pre induction measurement of cervical length (Rane et al., 2003).

In practice, cervical length is not used in clinical settings as an assessment of cervical ripening prior to IOL. This is likely due to lack of resources such as trained sonographers and adequate equipment. Additionally, and perhaps more importantly, its superiority over digital vaginal examination is not clearly proven.

Figure 1.13 Transvaginal ultrasonographic measurement of cervical length.

1.5.3 Posterior cervical angle

Another way to establish the cervical preparation for vaginal delivery is a sonographic measurement of posterior cervical angle. This measurement was created to improve the prediction of successful IOL followed by a vaginal delivery (Paterson-Brown et al., 1991).

This measurement is obtained during a transvaginal ultrasound scan, and it is meant to mimic a known Bishop score component of cervical position (posterior, mid, anterior). The transducer is inserted vaginally and placed approximately 3 cm away from the cervix to avoid unnecessary pressure which could change the shape of the cervix and affect accuracy of the measurement. Images of the cervix in a sagittal plane should be stored. Posterior cervical angle is an angle between the cervical canal and the posterior uterine wall (Paterson-Brown et al., 1991). The more acute the angle, the higher the chance of failed IOL (Paterson-Brown et al., 1991; Rane et al., 2004) .

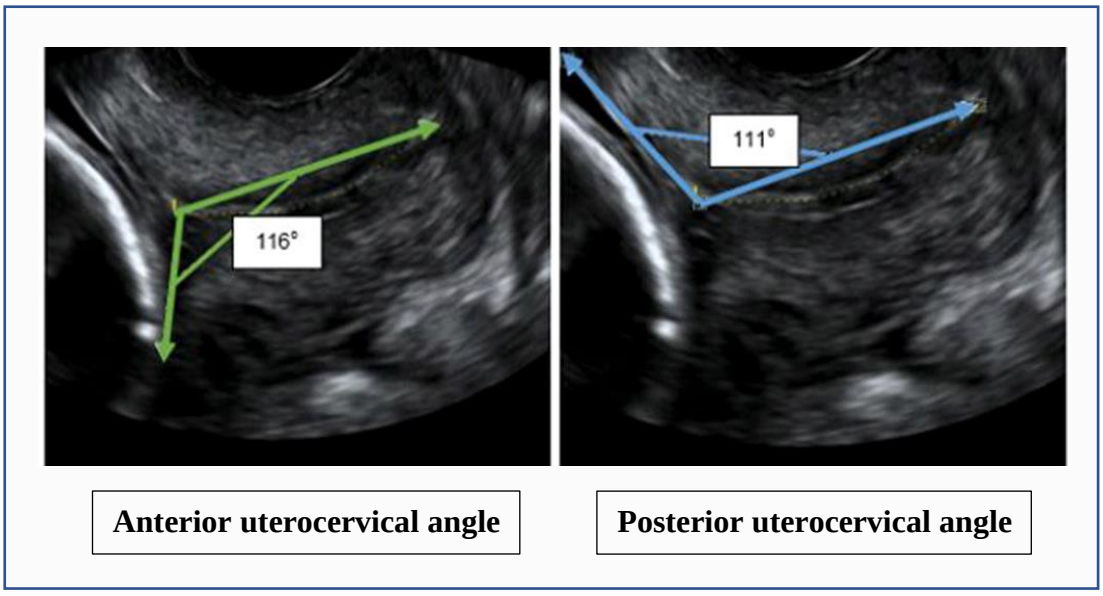


Figure 1.14 Transvaginal ultrasonographic measurement of posterior and anterior uterocervical angle. Image reproduced from poster presented by Tara Lynch at the American Journal of Obstetrics and Gynaecology. Poster session V in the Supplement to January 2019 release (Lynch et al., 2019)

1.5.4 Cervical consistency index

There is some evidence that cervical consistency could be assessed not only by vaginal examination as a component of the Bishop score but also via transvaginal ultrasound scan using the cervical consistency index (Parra-Saavedra et al., 2011). So far it has been used in prediction of preterm delivery rather than in the context of labour induction.

To obtain a cervical consistency index(CCI), cervical length should be measured using the standard technique described above (Pandis et al., 2001). The important detail is to avoid excessive pressure on the anterior lip of the cervix (Parra-Saavedra et al., 2011). The screen is then split and frozen on the image of the cervix on one side and the real time image on the other side can be adjusted. Soft pressure is then applied to a real time image until there is no further cervical shortening. The antero-posterior measurement of cervical thickness is obtained on both sides of the screen ensuring that the line between cervical length and thickness is at the 90° angle. A shorter measurement, called AP' is then divided by a longer measurement called AP and this ratio is multiplied by 100. This gives us an equation CCI=AP'/APx100 (Parra-Saavedra et al., 2011). The estimated detection rates of spontaneous PTB before 32, 34 and 37 weeks using CCI were 100%, 91% and 79% (63/80), respectively, for a 10% screen positive rate (Parra-Saavedra et al., 2011).

This measurement is complex and has not been validated in clinical settings as an adequate method of cervical ripening assessment prior to IOL. It is unlikely to be used widely on delivery suites around the country.

1.5.5 Cervical dilatation on ultrasound

Cervical dilatation on ultrasound is one of the newest methods of cervical assessment. It has been used mostly in the active phase of labour when the cervix is dilated to 4 centimetres or more. It has been described in 2009 (Zimerman et al., 2009) but so far has not been used outside of clinical trials. Originally, a 3D cervical volume technique was used. Several years later, a simple 2D transperineal ultrasound measurement was described (Hassan, Eggebo, et al., 2013) and proven to be feasible (Benediktsdottir et al., 2015; Hassan, Eggebo, et al., 2013; Yuce et al., 2015)

Cervical dilatation is measured using transperineal ultrasound technique, where the transducer is placed between the anus and the vulva using a transverse plane. Examination should start in a sagittal position followed by a 90-degree rotation to achieve a transverse view with appropriate landmarks. The probe is then tilted towards the anus to visualise the rectum and slowly tilted anteriorly until the cervix comes into the view. Once visualised, the cervix can be measured from side to side or antero-posteriorly (Wiafe et al., 2018).

The downside of transperineal ultrasonography is that it requires substantial training. However, it seems more acceptable to women who find vaginal examinations uncomfortable or intimidating (Benediktsdottir et al., 2015). There is evidence that repeated digital examinations may increase the risk of infection (Westover & Knuppel, 1995). Therefore, establishing an alternative assessment method of progress in labour would benefit patients and improve their satisfaction.

1.5.6 Angle of progression

Angle of progression is a reflection of fetal head descent in a birth canal (Barbera et al., 2009). Therefore, it is mostly used to monitor the progress of labour and chances of successful vaginal delivery in advanced first stage or in the second stage of labour when the cervix is fully dilated. It has also been used as an assessment prior to instrumental delivery and prediction of its success or failure (Bultez et al., 2016; V. Y. T. Chan et al., 2019).

Similarly, to sonographic cervical dilatation, angle of progression is measured using transperineal ultrasonography. The probe is placed between the labia majora, and the sagittal plane is obtained to visualise the symphysis pubis and a presenting portion of fetal head. Gentle rocking upwards might be required to clearly capture both structures. The angle between the long axis of symphysis pubis and fetal skull contour is measured (Barbera et al., 2009) (Figure 1.15).

The measurement of angle of progression similar to the station component in the Bishop score assessment. However, the landmarks here would be different as visualisation of maternal ischial spines is not possible on ultrasound. Interestingly, on the same plane as angle of progression, caput and even moulding can be assessed in advanced labour (Barbera et al., 2009; Hassan et al., 2015). As the clinical digital assessment of fetal head station during labour is known to be subjective (Buchmann & Libhaber, 2008; Dupuis et al., 2005), there is a need to compose a more reliable method with lower inter-observer variability. Researchers evaluated the accuracy of this technique concluding that there is a very small discrepancy between examiners (Barbera et al., 2009; Molina et al., 2010) which gives this method the potential of being more objective and reproducible (Usman et al., 2019).

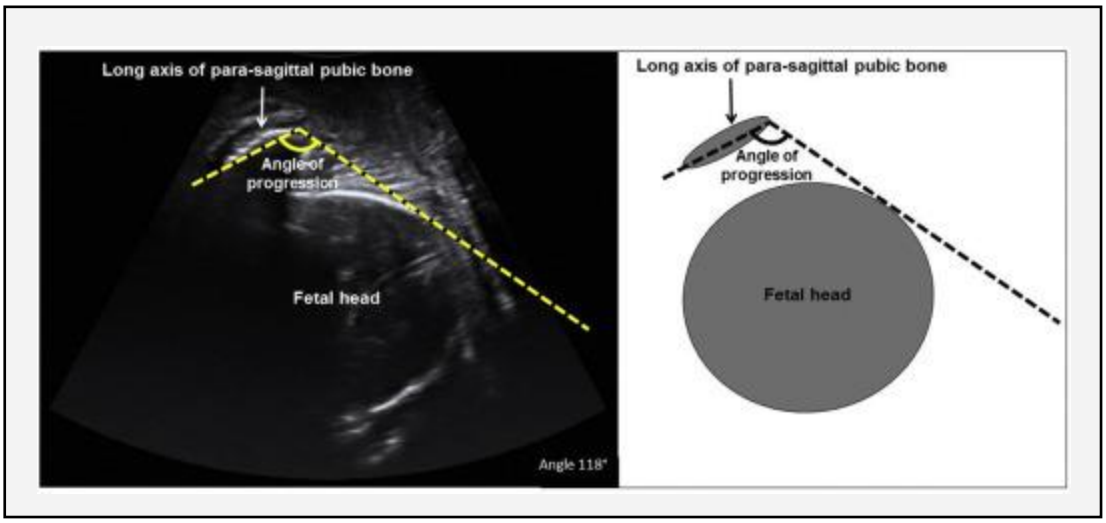


Figure 1.15 Transperineal ultrasonographic measurement of angle of progression.

1.5.7 Head to perineum distance

Head to perineum distance was described for the first time by Eggebo in 2006. It was used in women who ruptured their membranes prior to the onset of labour contractions as a tool to estimate the need for assisted operative delivery and the interval from the rupture of membranes to delivery (Eggebo et al., 2006). Repeated digital vaginal assessments or procedures such as speculum examination or a transvaginal scan can increase the risk of chorioamnionitis (Westover & Knuppel, 1995). Therefore, transperineal scan seems to be a safer approach. It could potentially be used as an objective way to establish fetal head station in the pelvic canal.

To obtain the measurement of head to perineum distance, the transducer is placed on the maternal perineum between the labia majora and the anus in a sagittal view and subsequently rotated 90° clockwise. The bony landmarks of adequate probe placement are the maternal ischial tuberosities. The probe should be held with firm pressure in transverse plane but without causing any discomfort to the patient. The shortest distance between the fetal head contour and maternal perineal skin is measured. Three measurements should be taken and a mean value calculated (Eggebo et al., 2006) (Figure 1.16).

Women with a head to perineum distance greater than 45mm before the onset of contractions seem to be at significantly higher risk of needing a caesarean section than those with a shorter measurement (Eggebo et al., 2006). This is in line with WHO

stages of head descent which describes the pelvic canal midpoint at the level of ischial spines. The distance from perineum to ischial spines measures approximately 5cm. According to various studies, head to perineum distance is an adequate method of evaluation of head engagement (Eggebo et al., 2006). It is well tolerated by patients, quick to perform, reproducible and relatively easy to learn (Benediktsdottir et al., 2018). Transperineal examination can predict vaginal delivery after IOL with similar efficacy as cervical length measurement or Bishop score. However, it does not seem to be good enough to justify its use as the only method for predicting the mode of delivery in clinical settings (Eggebø et al., 2008) .

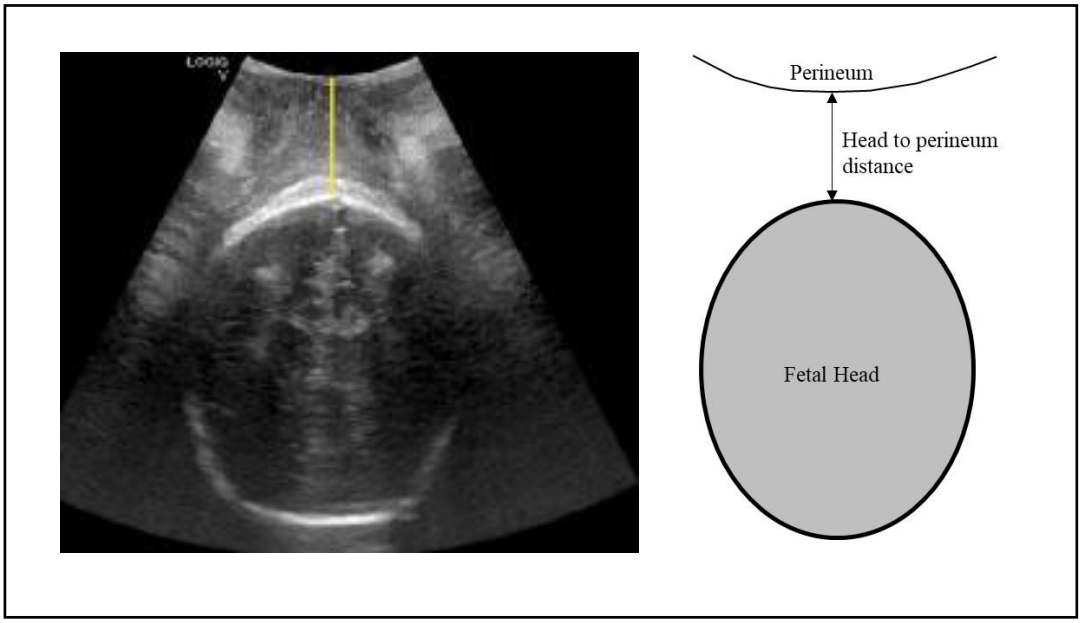


Figure 1.16 Transperineal measurement of head to perineum distance.

1.6 Prediction of adverse outcomes

Adverse outcomes

Adverse outcomes following labour induction can be defined in various ways. They can be divided into two groups of maternal and neonatal. In terms of maternal adverse outcomes, it could be a failure of achieving a vaginal delivery following IOL or even a failed IOL as such, when a woman does not go into labour despite clinicians' efforts to start the uterine contractions and cervical ripening process. Both outcomes result in delivery by caesarean section due to lack of progress. Another definition could be a suspected fetal distress, which often results in caesarean section in order to avoid devastating neonatal complications including an ischemic brain injury. In this case, caesarean section would be a maternal outcome and fetal distress resulting in hypoxia, could be described as an adverse neonatal outcome. Various studies use different definitions of adverse neonatal outcomes, but the majority would use cord pH, Apgar score following delivery, admission to NICU or confirmed diagnosis of hypoxic brain injury.

Successful vs failed induction of labour

The definition of successful IOL varies between authors and centres. Some, consider successful labour induction when a woman achieves a vaginal delivery following the process. Others, when a woman reaches an active stage of labour. Sometimes, the definition contains a time limit within which delivery should be achieved. Failed IOL should be defined as an unsuccessful vaginal delivery. However, it should not be

confused with failure to progress (Marconi, 2019). There are many factors contributing to successful or failed IOL.

1.6.1 Maternal factors

Maternal body habitus, body mass index, maternal age and medical comorbidities are amongst the most important factors predicting successful or failed IOL.

Obesity

Obesity is becoming an increasing problem in the UK. According to NHS Digital and National Statistics on Obesity, Physical Activity and Diet, 63% of adults in England were overweight or obese in 2018. The maternal obesity executive summary reports that 5% of women who book their pregnancy has a BMI of 35 or greater. This translates into almost 38500 maternities every year in the UK and carries substantial risk to the mother and the fetus. In addition to an increased risk of pregnancy loss (Lashen et al., 2004) hypertensive disorder (O'Brien et al., 2003; Weiss et al., 2004), diabetes mellitus (Weiss et al., 2004) and thromboembolism (Jacobsen et al., 2008; Larsen et al., 2007), obesity increases the chance of dysfunctional labour, prolonged first and second stage of labour (Carlson et al., 2015) as well as the need for labour induction (Usha Kiran et al., 2005).

Maternal obesity is associated with a higher rate of post term pregnancies as well as prolonged IOL with higher doses of acting agents being required (Ellis et al., 2019).

The physiology of parturition is altered by metabolic dysregulation in 70% of obese women. Adipose tissue secrets hormones such as leptin, apelin and visfatin which are essential for fluid haemostasis and glucose regulation (Carlson et al., 2015). In normal pregnancies leptin is released from the placenta via the inflammatory pathway and stimulates prostaglandin E2. Elevated leptin levels in obese women not only cause chronic inflammation but could also desensitise maternal tissue to PGE2 surge in early labour (Suidan et al., 2015). This disturbs a physiological progesterone withdrawal and prostaglandin activation (Konopka et al., 2013). Cervical ripening is thought to be altered by high leptin levels which impair collagen degradation and cervical cells degeneration. This concept could explain a lower Bishop score in obese women at term when compared to women with normal body weight (Zelig et al., 2013). The process of IOL usually takes longer and often requires higher doses of prostaglandins and oxytocin (Ellis et al., 2019). There is some evidence that obese women have lower numbers of oxytocin receptors within uterine myometrial cells. Therefore, they are less responsive to natural but also synthetic oxytocin. This leads to a more difficult augmentation of labour and uncoordinated, short-lasting contractions (Carlson et al., 2015).

Therefore, obese women with high body mass index, have a lower rate of successful vaginal deliveries following IOL and higher rate of caesarean sections for failure to progress (Ellis et al., 2019; Gibson & Waters, 2015; Weiss et al., 2004). The overall risk of adverse perineal outcomes including assisted vaginal delivery, postpartum haemorrhage, anal sphincter injury and low Apgar score is substantially higher in these

women (Jardine et al., 2020; Prosser et al., 2018). Unlike age or ethnic origin, maternal weight is a modifiable risk factor and all health professionals working in maternity services should actively encourage obese women to lose weight in order to avoid unwanted complications in pregnancy.

Maternal age

Advanced maternal age, often defined as greater than 35 years, is a significant risk factor for several obstetric complications including stillbirth, as described above. Older women seem to have a higher caesarean section rate for failed IOL when compared to younger women in otherwise low risk pregnancies (Batinelli et al., 2018). The probability of normal birth without any intervention or sustaining a complication is inversely proportional to maternal age (Prosser et al., 2018).

Dunn et al, calculated that the majority of women classified as an advanced maternal age group, deliver vaginally following IOL. However, there is an independent, age related, two-fold increase in operative delivery via caesarean section (L. Dunn et al., 2017). The relationship between maternal age and caesarean section rate seems to be linear from the age of 16. The older the mother, the higher the risk of needing an operative delivery. This is also true for multiparous women who have a history of successful vaginal delivery. Their risk of caesarean section rises by one third with every 5 year increase in age (Smith et al., 2008).

Maternal age is associated not only with mode of delivery and the outcome of IOL but also with spontaneous contractile activity which is likely related to the length of labour. Older women were found to have reduced uterine contractility which resulted in impaired uterine function and prolonged labour. The mean labour duration gradually increases from the age of 16 until 35 when it reaches the plateau. The prolongation of labour is calculated as 0.49 hours with every 5 years above the age of 16. The leading cause for failed IOL and subsequent caesarean section seems to be prolonged labour and altered myometrial contractility rather than fetal distress (Smith et al., 2008).

A large UK based risk classification study which analysed the data from over 320.000 deliveries found that women in the age group from 35 to 44 years old have an intermediate or increased risk for complications such as assisted vaginal delivery, caesarean section, obstetric anal sphincter injury, haemorrhage and low Apgar score regardless of any pre-existing medical co-morbidities (Jardine et al., 2020).

Parity

Multiparity with a history of previous vaginal birth is one of the strongest predictive factors for a successful vaginal delivery following IOL (Batinelli et al., 2018; Feghali et al., 2015; Fiolna et al., 2019; Jardine et al., 2020; Prosser et al., 2018; Rane et al., 2003). For instance, this has been examined on women undergoing IOL before 37 weeks gestation. These procedures have a high failure rate, especially when very premature. Parous women, however, were significantly more likely to deliver vaginally following preterm IOL when compared to nulliparous women with an odds

ratio of 6.78 (Feghali et al., 2015). Additionally, time interval from induction to delivery and overall labour duration was two to three times shorter in parous women (Hoffman et al., 2006; Vahratian et al., 2005).

A large project which aimed to calculate the risk of labour complications, including operative delivery, either assisted vaginal delivery or caesarean section, postpartum haemorrhage, obstetric anal sphincter injury or Apgar score lower than 7 at five minutes of life, took place in the UK. Data from 87 hospitals across the country was analysed in line with the NICE guideline for intrapartum care. Parous women who exclusively delivered vaginally before, were found to have the lowest risk of adverse outcomes listed above. The rates varied from 9% to 22% depending on pre-existing risk factors such as maternal age, BMI and various medical or obstetric conditions. Nulliparous women had a significantly higher rate of quoted complications, ranging from 43% to 64% which was comparable to parous women who previously delivered by caesarean section (43% to 66%) (Jardine et al., 2020).

Physiologically, oxytocin which is a hormone responsible for the onset and acceleration of labour has a more significant effect in multiparous women. Animal studies have shown that this phenomenon is caused by a higher number of oxytocin receptors in the maternal brain, especially in the hypothalamus which is responsible for self-regulation. This results in more effective positive feedback and subsequently leads to more efficient labour, birth and lactation in parous women (Blanks et al., 2007; Brummer, 1972; Xu et al., 2013). Interestingly, nulliparous women have a higher level

of oxytocin in late pregnancy which could potentially be responsible for lower sensitivity and a decreased number of oxytocin receptors when compared to multiparous women (Boksa, 1997; Terzidou et al., 2011). Additionally, enhanced positive feedback in parous women adds momentum to labour contractions and once they are established, interruption is less likely. This would explain why multiparous women require less intervention in labour when compared to first time mothers (Hertelendy & Zakár, 2004; Seppälä & Vara, 1972). This includes augmentation of labour with synthetic oxytocin, artificial rupture of membranes or operative birth.

Gestational age

Generally, the higher gestational age, the greater chance for spontaneous onset of labour as well as for successful labour induction (Nassar et al., 1998). Women who underwent IOL before 34 weeks gestation had a higher failure rate than those induced after 34 weeks. However, the majority of women whose labour was induced prematurely for various medical or obstetric reasons, delivered vaginally (Feghali et al., 2015). The mean gestational age of women achieving a vaginal delivery was 38.4 weeks versus 37.9 weeks for those who required caesarean section following IOL (Giugliano et al., 2014).

Gestational age correlates closely with fetal size. The later in pregnancy, the greater fetal weight and higher risk of vaginal delivery failure (Gibson & Waters, 2015). Nulliparous women with a new-born weighing over 3500g had significantly higher risk of caesarean section for failure to progress following IOL (OR 1.66). This risk

was even greater with birthweight over 4000g (OR 2.38) (Vrouenraets et al., 2005). There are some studies suggesting that elective IOL at 39 weeks gestation in low risk population increases the chances for normal vaginal delivery (Cheng et al., 2012; Grobman et al., 2018)

Preterm IOL may be required for multiple obstetric complications such as fetal growth restriction. In these patients, prolonged gestational age could lead to hypoxia and even result in stillbirth. Careful planning of delivery is essential to balance the neurological adverse outcomes, consequences of prematurity and failed IOL versus potential acidosis and fetal distress (Li et al., 2020).

1.6.2 Cervical measurements

Bishop score

Bishop score was originally designed to assess the interval between vaginal examination and spontaneous onset of labour (Bishop, 1964). Currently it is the most commonly used cervical assessment prior to induction and in latent phase of labour. A score of ≥ 6 is considered favourable and describes a ripe cervix. The chances of successful IOL for women with BS >8 are comparable to women in spontaneous labour. A Bishop score of less than 6 indicates an unfavourable cervix. IOL is usually longer in women with a lower Bishop score (Wormer et al., 2021).

Prediction of successful vaginal delivery based on Bishop score alone has a good sensitivity of 75% and positive predictive value of 83%. However, its specificity and

negative predictive value are low (Wormer et al., 2021). This means that by using the above scoring system we are likely to be able to correctly identify those women whose IOL will be successful based on the high BS but our prediction of failure is going to be a lot less accurate (Gibson & Waters, 2015). Since 1964 the original scoring system has been modified multiple times, but this has not improved the predictions (Laughon et al., 2011).

Various studies have examined the performance of Bishop score in prediction of operative delivery following IOL. Women with a favourable cervix have been shown to have similar risk of caesarean section for failure to progress following IOL as those who awaited spontaneous onset of labour (Nielsen et al., 2005). The odds ratios for caesarean delivery following IOL were 1.7 for women with BS ≥ 6 and 2.8 for those with BS < 6 when compared to spontaneously labouring women (Yeast et al., 1999). Risk of caesarean section for nulliparous women in spontaneous labour, those induced with favourable and unfavourable cervix was 14%, 17% and 43% respectively (Vahratian et al., 2005).

Bishop score is a cheap and reproducible assessment method, but it fails to give a personalised prediction of the mode of delivery. It simply puts women into two categories of those with a ripe and unripe cervix. This however, does not reflect on the outcome as most women from both groups will deliver vaginally (Grobman et al., 2018). Because of the previously described limitations, numerous attempts have been

made to incorporate other methods of cervical assessment in order to create a reliable and individualised model to predict the mode of delivery.

Cervical length

Ultrasonographic cervical length assessment correlates well with the timing of labour. Typically, the shorter the cervix, the greater the chance of spontaneous uterine contractions (Grobman et al., 2018). Its use has been established in the prediction of preterm birth (Sonek & Shellhaas, 1998) but many studies have evaluated its performance in forecasting the adverse outcomes such as caesarean section following IOL. Additionally, women find a transvaginal scan more tolerable and significantly less painful than vaginal examination (Tan et al., 2007).

There is divergent evidence on the accuracy of predicting the chance of successful vaginal delivery or a risk of caesarean section following IOL based on cervical length measurement. Some studies report that both (Baños et al., 2015), Bishop score of less than 5 and cervical length measurement of more than 20mm has a potential to predict delivery by caesarean section following IOL with an area under the curve of 0.607 vs 0.611. The latter has slightly higher sensitivity, positive and negative predictive value, 64% vs. 80%, 27% vs. 30% and 83% vs. 89% respectively (Tan et al., 2007).

Some authors suggest that cervical length can provide a better estimation of the chances for successful or failed IOL when compared to Bishop score (Kehila et al., 2016; Kehila et al., 2015; Pandis et al., 2001; Rane et al., 2003). While others, claim

that transvaginal cervical length assessment is a poor predictor of labour induction outcomes (Roman et al., 2004a) (Park, 2007; Roman et al., 2004b). Few groups have incorporated cervical length measurement into predictive models together with variables such as maternal factors and other ultrasonographic parameters (Kamel et al., 2021; Pereira et al., 2014; Prado et al., 2016; Rane et al., 2004)

A systematic review and metanalysis performed in 2007 which included 20 citations and over 3100 participants concluded that cervical length measurement was not effective at predicting mode of delivery. Surprisingly, however, it predicted successful IOL with a likelihood ratio of positive test of 1.66 and failed IOL with likelihood ratio of negative test of 0.51 (Hatfield et al., 2007). Another, larger systematic review from 2013 included 31 studies and deducted that cervical length measurement has a moderate potential of predicting caesarean section with sensitivity ranging from 0.14 to 0.92 and specificity ranging from 0.35 to 1 depending on the study. A summary receiver operating characteristics curve proved a constrained predictive value which is too low to offer women caesarean section, a procedure which carries significant risks, without a trial of vaginal delivery (Verhoeven et al., 2013).

Posterior cervical angle

Posterior cervical angle is another sonographic measurement which has been examined by various research groups with a hope that it could improve the prediction of the mode of delivery following IOL.

In 1991, Paterson-Brown has described the novel transvaginal cervical assessment method and established that patients requiring caesarean section had an acute PCA with a median of 60 degrees and those who delivered vaginally had a wider PCA with a median of 90 degrees (Paterson-Brown et al., 1991).

Another group has chosen a posterior cervical angle cut off of 120 degrees to distinguish women who were likely to have a successful IOL from those who required an operative delivery. Posterior cervical angle above 120° was associated with vaginal delivery. The narrower angle, not only significantly increased the risk of an emergency caesarean section but also, predicated a prolonged labour. Additionally, Rane's group incorporated PCA measurement together with a sonographic assessment of occiput position and maternal characteristics into a predictive model and was able to significantly improve receiver – operating characteristics (ROC) curves when compared to Bishop score in the prediction of vaginal delivery within 24h of labour induction (Rane et al., 2004).

Al-Adwy suggested that the posterior cervical angle above 99.5° increases the woman's chance of successful IOL and it was more reliable than a Bishop score of ≥ 5 or cervical length of < 34mm (Al-Adwy et al., 2018). Despite differences in cut off, all of the studies suggested that PCA has a potential to improve prediction of mode of delivery following IOL when compared to traditional vaginal assessment of Bishop Score. General rule applies, the more acute angle, the greater the risk of operative delivery via caesarean section.

Cervical dilatation on ultrasound

Measurement of sonographic cervical dilatation has been originally described as a part of transperineal sonographic assessment on a small number of patients with the aim of establishing an alternative to digital vaginal examination. The measurement proven to be reproducible and reliable with a mean difference between digital and ultrasonographic measurements of 0.08cm (Hassan, Eggebo, et al., 2013). Subsequently, this method was examined on a larger cohort of over 300 women as a part of prediction model for caesarean section delivery following IOL. In univariate regression analysis, sonographic cervical dilatation was statistically significant with odds ratio of 0.33. However, this has not been confirmed by the multivariate regression model (W. W. Y. Chan et al., 2019).

Angle of progression

Angle of progression is a measurement obtained during transperineal ultrasound. It has been designed to minimalize the discrepancy between clinicians in assessing fetal head station during labour and make it more reliable. Authors aimed to predict the mode of delivery in spontaneously labouring patients (Barbera et al., 2009).

Angle of progression greater than 120° was associated with successful vaginal delivery. Additionally, it was consistent with a head engagement on vaginal examination. Based on angle of progression, mean time from assessment to delivery

was estimated with the shortest time of 5.8 min +/- 1.65 for angles greater than 200° (Barbera et al., 2009).

Subsequent studies provided more details on AOP prediction of labour progression. In the first stage of labour when the cervix was actively dilating each 1° increase in the angle, improved chances of successful vaginal delivery by almost 24%. The same increase in AOP in the second stage, when the cervix was fully dilated, caused a 35% increase in the chances of succeeding with a vaginal birth. An interesting correlation was found on the regression curve which suggested that there could be an increase of 1cm in cervical dilatation with each 5° increase in the angle of progression (Marsoosi et al., 2015). The same authors published the results of the area under the curve for prediction of successful vaginal delivery in the first and second stage of labour which was 0.88 and 0.95 respectively.

Various studies obtained slightly different cut-off points for accurate prediction of mode of delivery. In the original study, all patients with AOP greater than 120° achieved a vaginal delivery (Barbera et al., 2009). It was confirmed by Kalache's group that AOP $\geq$ 120° was associated with a successful assisted or spontaneous vaginal delivery in 90% of cases (Kalache et al., 2009). In Marsoosi's study, the angle of progression greater than 113° and fetal head in occipito-anterior position were warrants of successful vaginal delivery in almost 91% of patients (Marsoosi et al., 2015).

Levy's group went one step further and measured AOP in patients at ≥ 39 of gestation prior to onset of labour. All of the recruited patients delivered within one week of assessment. An acute angle of progression of less than 95° in nulliparous women was predictive of caesarean section. However, the same cut-off did not correlate with the mode of delivery in parous women. Interestingly, parous women had narrower AOP before the onset of contraction when compared to nulliparous women, 98° vs 104°, respectively. This, however, did not corelate with the mode of delivery and most multiparous women delivered vaginally. It only highlights parity as a strong independent factor for successful vaginal delivery (Levy et al., 2012).

A very recent study has incorporated AOP into the prediction model for perinatal outcomes following IOL. Authors found that AOP at rest was one of the independent predictors for caesarean section in multivariate logistic regression analysis with an odds ratio of 0.9 (Kamel et al., 2021). Few studies reported that an area under the receiver operating characteristic curve for prediction of successful vaginal delivery was higher for angle of progression than for a digital examination (Levy et al., 2012; Marsoosi et al., 2015; Torkildsen et al., 2011).

Head to perineum distance

Head to perineum distance is one of the transperineal measurements introduced to assess women's readiness for labour in a minimally invasive way to reduce the risk of infection (Eggebo et al., 2006).

In the original article, HPD of 45mm was significant for prediction of mode of delivery. Women with HPD > 45mm went into labour later than those with shorter measurements, more frequently requested epidural analgesia and had higher risk of caesarean section (Eggebo et al., 2006). Similar results were obtained by another group which established that head to perineum distance ≥ 43mm is predictive of assisted vaginal delivery or caesarean section with 89% sensitivity and 69% specificity (Carvalho Neto et al., 2019). Subsequent study by these authors, positively correlated HPD of 4.17 +/- 0.54cm with surgical delivery including forceps and caesarean section (Carvalho Neto et al., 2021). There was an attempt to predict time to delivery based on the prelabour assessment of head to perineum distance. However, it has proven ineffective (Chan et al., 2021)

Eggebo further evaluated HPD performance in women undergoing IOL. HPD of < 40mm was established to be predictive for successful vaginal delivery and its performance matched the one of Bishop score and cervical length. However, none of the above assessments' prediction value was high enough to be used in clinical settings. Authors elaborated that parity is the best predictive factor for vaginal delivery following IOL (Eggebø et al., 2008). These finding were confirmed in another study which reported that all patients with HPD < 40mm achieved vaginal delivery following IOL and whose who had HPD > 61mm required caesarean section (Ali & Hebbar, 2019).

1.6.3 Doppler studies

The Doppler ultrasound has been used for fetal well-being assessment since 1977 (FitzGerald & Drumm, 1977). It is a non-invasive method of examining the blood flow in major blood vessels such as umbilical artery (UA), middle cerebral artery (MCA) or ductus venosus (DV). Doppler signal assesses the impedance to flow within a blood vessel which reflects oxygenation (Nicolaides et al., 1988).

Flow velocity waveforms created by the changing frequency of the Doppler signal have a characteristic pattern depending on the fetal cardiac activity, blood vessel elasticity and peripheral resistance. For instance, the umbilical artery waveform in a healthy pregnancy represents a pattern of a low-resistance system characterised by a forward flow throughout the cardiac cycle (Neilson, 1987). In cases of placental insufficiency, the circulation between the fetus and the placenta is progressively affected. The Doppler pulsatility index (PI) increases reflecting the vascular disease. Noticeable changes within Doppler indices are observed when three quarters of the placental blood vessels obliterates, representing significant vascular disease (Thompson & Trudinger, 1990).

On the other hand, the middle cerebral artery Doppler waveform is typical of a high-resistance system and the impedance to blood flow tends to decrease as a consequence of worsening placental insufficiency. This so called “brain sparing” effect represents fetal coping mechanisms and blood flow redistribution to preserve the most vital

organs such as brain, heart, and adrenal glands from hypoxia (Hecher et al., 2001; Scherjon et al., 1993). Cerebroplacental ratio (CPR) is the MCA PI to the UA PI ratio and has been described in 1983 by Arbeille (Arbeille et al., 1983). It is thought to be more accurate in the prediction of adverse perinatal outcomes than individual Doppler measurements (Gramellini et al., 1992; Karlsen et al., 2016). It has been widely examined in pregnancies complicated by fetal growth restriction for the prediction of adverse perinatal outcomes such as perinatal mortality, assisted vaginal delivery or caesarean section for suspected fetal distress, admission to Neonatal Intensive Care Unit (NICU), low Apgar score at fifth minute of life (Bahado-Singh et al., 1999; DeVore, 2015; Garcia-Simon et al., 2015; Karlsen et al., 2016). There is growing evidence that the cerebroplacental ratio is also useful in the prediction of adverse perinatal outcomes in appropriately grown fetuses (Moreta et al., 2019) (Prior et al., 2013).

The Cochrane review compared the outcomes of high-risk pregnancies which were monitored with an umbilical artery Doppler to those who did not undergo any monitoring. There were fewer perinatal deaths (12 in 1000 vs 17 in1000), fewer stillbirths (6 in 1000 vs 9 in 1000), fewer newborns with Apgar score < 7 in fifth minute of life (26 in 1000 vs 29 in 1000) fewer inductions of labour (298 in 1000 vs 334 in 1000) and fewer caesarean sections (237 in 1000 vs 263 in 1000) in the UA Doppler group (Alfirevic et al., 2017).

Low CPR as well as its individual components - high PI in UA and low PI in MCA were investigated in women who reported reduced fetal movements. All of the above measurements were related to adverse perinatal outcomes, such as lower pH in cord blood gas, lower Apgar score in first minute of life and higher rate of admission to NICU when compared to women who did not report RFM (Eshraghi et al., 2020).

Prior's group has examined the performance of cerebroplacental ratio in the prediction of intrapartum fetal distress in low-risk population. Women were assessed within 72 hours of delivery, PI in UA and MCA was measured. The clinicians attending delivery were blind to the results and the care provided was the standard obstetric care. Infants delivered vaginally, by SVD had significantly lower UA PI (0.76) when compared to those who delivered via emergency caesarean section for suspected fetal compromise (0.86) (Prior et al., 2013).

A systematic review which included 21 studies have concluded that the measurement of CPR is strongly associated with adverse perinatal outcomes. Women with low CPR were reported to have meconium stained liquor, abnormal CTG in labour and low pH in cord blood samples after delivery more frequently than those whose Doppler indices were normal (Liam Dunn et al., 2017). Subsequent meta-analysis and systematic review found similar correlations. However, the authors found large discrepancies in reported sensitivities and specificities in the individual studies and called for more clinical trials. The better predictive accuracy of CPR when compared to UA PI was emphasized (Vollgraff Heidweiller-Schreurs et al., 2018). The usefulness of CPR in

the identification of pregnancies at risk of operative delivery (RR 2.52), admission to NICU (RR 2.23), or hypoxia (RR 1.19) was rectified by another systematic review (Moreta et al., 2019). CPR, as well as MCA and UA Doppler was used in prediction of stillbirths. CPR was found to be the best predictor out of the three, but its performance was still poor (DR 32%, FPR 10%). The performance accuracy of CPR was followed by MCA PI with DR of 29% and FPR of 10% (Morales-Roselló et al., 2020).

1.6.4 Biochemical markers

Placental growth factor

Placental growth factor (PLGF) is a member of the vascular endothelial growth factor family which is released by a variety of body cells and takes part in angiogenesis. PLGF is released by number of human tissues including thyroid, heart, lung, liver, bone and skeletal muscle. In pregnancy, the placenta is responsible for PLGF expression which is crucial for fetal development and growth (Chau et al., 2017). This expression increases significantly in the second trimester due to spiral arteries remodelling to support rising fetal demands. PLGF inhibits trophoblastic cells apoptosis and facilitates their proliferation. It results in a significant increase in utero placental circulation (Arroyo et al., 2014). The concentration of PLGF is low in the first trimester of pregnancy and increases gradually until 30 weeks when it peaks (Figure 1.17).

PLGF levels rise in certain pathological processes such as neoangiogenesis, the blood vessel formation supporting growth and metastasis of malignant tumours (Grimm et al., 2009). Additionally, PLGF may promote an inflammatory response instead of an angiogenic reaction, which is called inflammatory switch. This phenomenon has been observed in cases of missed miscarriage, pregnancies complicated by preeclampsia (Nejabati et al., 2017) as well as those with fetal growth restriction (Arroyo et al., 2014). In pathological conditions, hypoxia stimulates PLGF expressions by various body cells including keratocytes, retinal epithelium or cardiomyocytes (De Falco, 2012).

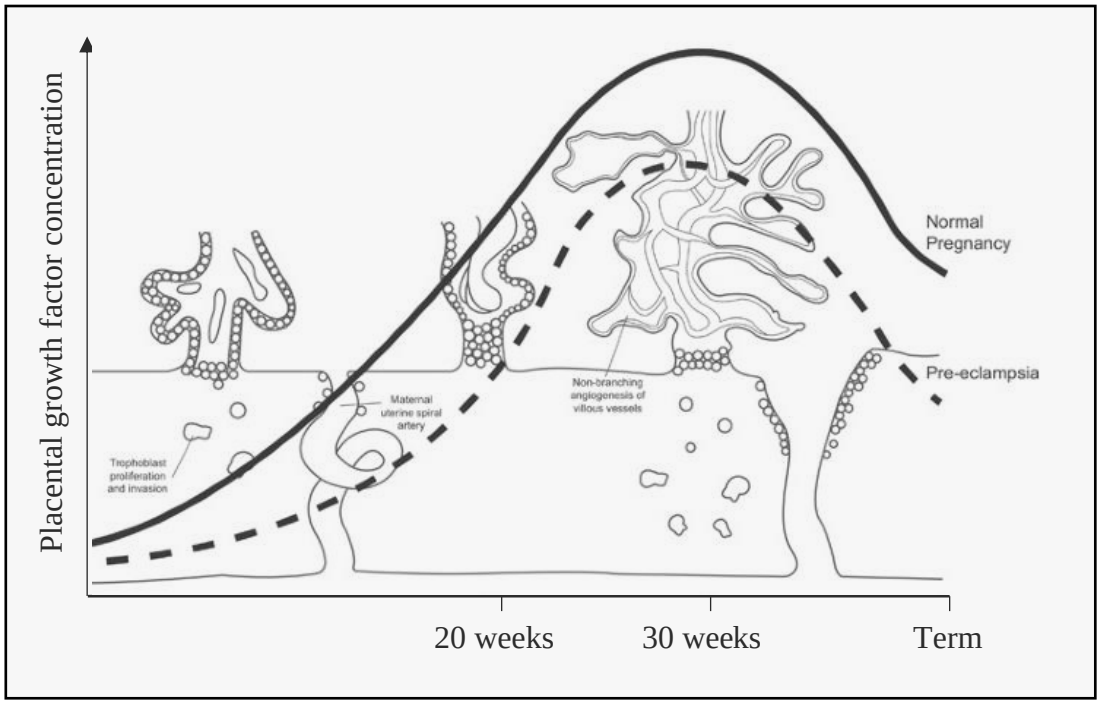


Figure 1.17 Circulating PLGF concentrations in normal pregnancy vs pregnancy complicated by preeclampsia (Reprinted by permission from Springer Nature, Journal of Human Hypertension) (Chau et al., 2017).

Decreased serum levels of PLGF were noted in pregnant women who subsequently developed preeclampsia (Levine et al., 2004). PLGF based testing has been introduced by NICE into the updated Hypertension in pregnancy guideline (NICE NG 133, 2019). Two PLGF isomers, PLGF-1 and PLGF-2 were examined at 20-24 weeks and 30-34 weeks gestation in order to identify a better predictor of pathological pregnancies including those complicated by preeclampsia or SGA and showed that their performance was similar (Nucci et al., 2014b). In pregnancies affected by trisomy 13, 18 or 21 but also by preeclampsia, decreased levels of PLGF-1 at 11 to 13 weeks were more pronounced when compared to PLFG-2 levels (Nucci et al., 2014a)

Researchers have been searching for a reliable method of prediction and diagnosis of intrapartum fetal hypoxia. An Australian group examined over 200 low risk women fortnightly from 36 weeks onwards and found that patients who required a caesarean delivery for suspected fetal distress and those whose infants had low cord pH, low Apgar score or were admitted to NICU, had lower PLGF (Bligh et al., 2018).

A systematic review of PLGF levels in pregnancies after 20 weeks gestation as a predictor of adverse perinatal outcomes showed, that low level of this proangiogenic protein was associated with pregnancy complications such as fetal growth restriction (Sherrell et al., 2018). Some authors reported that PLGF was significantly lower in pregnancies affected by placental insufficiency when compared to those who were constitutionally small and to appropriately grown controls (Benton et al., 2012).

Various groups tried to address the utility of PLGF testing in the prediction of other adverse neonatal outcomes but the results were conflicting (Sherrell et al., 2018)

Soluble Fms-like tyrosine kinase-1

Tyrosine kinase is an antiangiogenic protein which binds to VEGF and PLGF particles opposing their effect on blood vessel formation and growth. sFLT-1 is a receptor which binds to VEGF and PLGF reducing their serum concentration (Khalil et al., 2008). This potent PLGF antagonist is produced by different organs including the human placenta (Clark et al., 1998). Serum concentration of sFLT-1 in uncomplicated pregnancy is low throughout first, second and early third trimester. It rises after 33 weeks gestation as a result of vascular growth and placental aging (Schrey-Petersen & Stepan, 2017).

Administration of sFLT-1 to pregnant rats caused clinical and pathophysiological changes typical for preeclampsia such as hypertension, proteinuria and glomerular endotheliosis (Maynard et al., 2003). sFLT-1 concentration is elevated in women whose pregnancies are affected by preeclampsia and the sFLT-1 to PLGF ratio has been suggested for screening and diagnosis of preeclampsia (Schrey-Petersen & Stepan, 2017; Zeisler et al., 2016). sFLT-1 concentration rises 5 weeks prior to the onset of the disease, and it is associated with the clinical severity of the condition. Levels normalise promptly following delivery of the placenta (Levine et al., 2004). Older women (>35yo) have significantly higher serum concentration of sFLT-1 in pregnancy. This could potentially represent oxidative stress related to higher risk of

adverse perinatal outcomes in this population (Odame Anto et al., 2018) (Figure 1.18). However, this hypothesis requires further research.

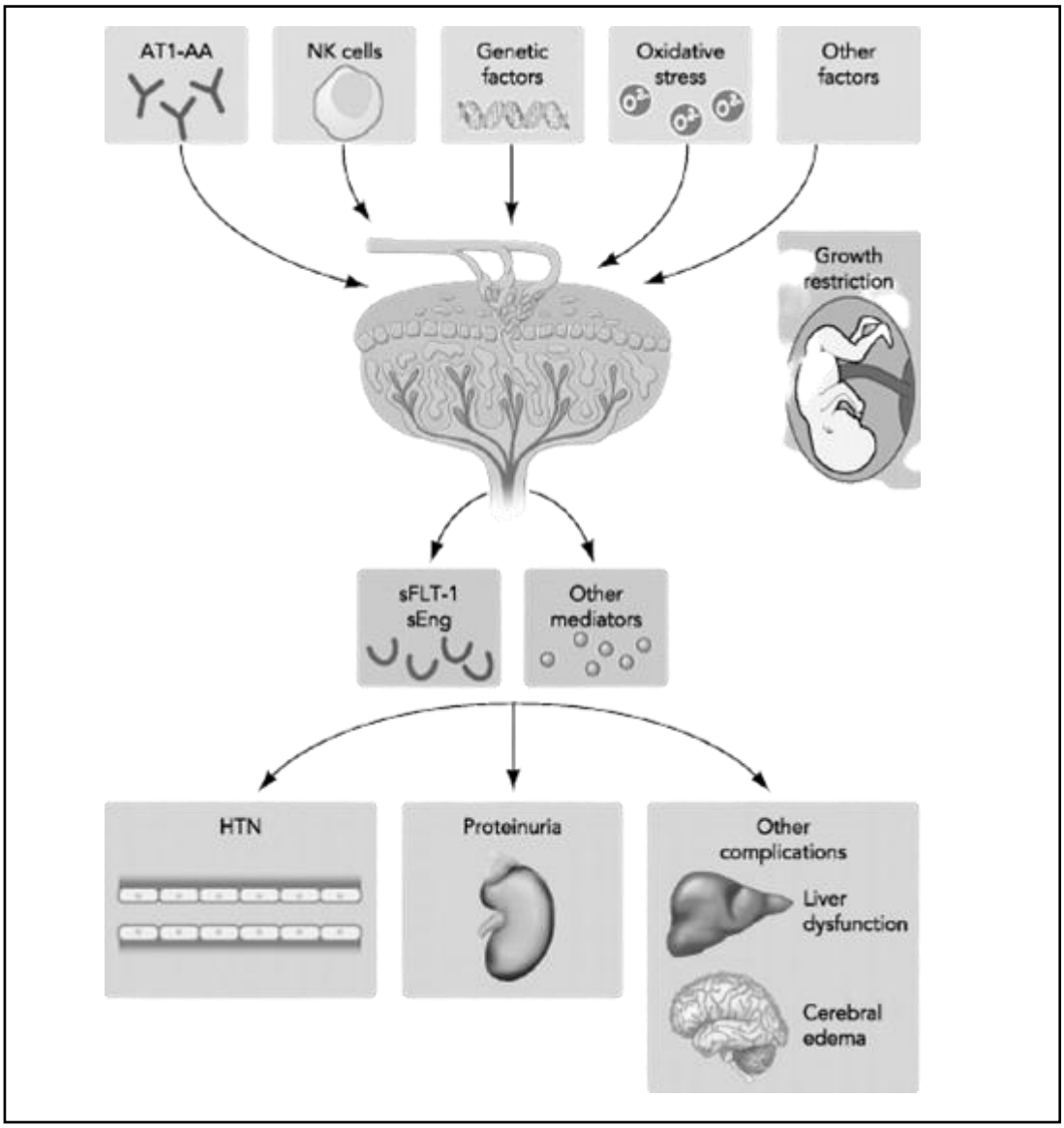


Figure 1.18 Pathophysiology and features of preeclampsia. Altered angiogenic factors indicating placental dysfunction can result in diverse adverse pregnancy outcomes. Reprinted from (Wang et al., 2009) with permission. Copyright ©2009, American Physiological Society.

1.6.5 Literature review conclusion

This literature review included all methods of IOL used in clinical practice. All methods have their individual risk and benefits; in general, pharmacological methods are used in primiparous women or multiparous women with a history of previous vaginal birth and mechanical methods are recommended for women with a history of previous caesarean section or any other uterine surgery. Mechanical methods could also be used in women who previously experienced hyperstimulation secondary to the use of prostaglandins. Oral Misoprostol is not used in the UK for IOL for maternal or fetal indications due to its safety profile and higher hyperstimulation rate when compared to other induction methods. It is however used in cases of in utero fetal demise and it seems to be the most effective in these situations.

I have tried to undertake an extensive literature review and encompass all methods as well as indications for IOL. The list is not exhaustive, but it includes the most common maternal and fetal indications recognised and supported by professional bodies such as the RCOG and ACOG. The most common indication for IOL was a post-date pregnancy.

The Bishop score is the most commonly used clinical assessment prior to IOL. Unfortunately, it is subjective and has significant inter- and intra-observer variability. Its utility at predicting induction-to-delivery interval and mode of delivery is limited. The literature review highlighted that successful vaginal delivery can be predicted

from maternal characteristics and components of obstetric history. This prediction can be enhanced by the addition of pre-induction measurement of cervical length by transvaginal ultrasound scan. The novel transperineal measurements such as head to perineum distance and angle of progression could potentially be used to improve this prediction further.

There is good evidence that cerebroplacental ratio can reflect prelabour fetal oxygenation. So far, this assessment has been used in risk stratification for fetal hypoxia in small for gestation age fetuses. Biochemical factors such as PLGF and sFLT have been found to be useful predictors of preeclampsia and so called placental angiogenic syndrome related to various placental and maternal cardiovascular complications. -So far, PlGF/sFLT ratio has not been examined in the context of labour induction and prediction of adverse maternal and neonatal outcomes.

Chapter 2

LIST OF PRESENTATIONS AND PEER-REVIEWED PUBLICATIONS

2 CHAPTER 2: LIST OF PRESENTATIONS AND PEER-REVIEWED PUBLICATIONS

1. "Pre-Induction prediction of Caesarean section for failure to progress". In June 2017, I gave an oral presentation at the 16th World Congress in Fetal Medicine in Ljubljana, Slovenia. The presentation contained prediction model described in chapter 4 and chapter 5 of this thesis.

2. "Prediction of adverse perinatal outcomes by the cerebroplacental ratio in women undergoing IOL". In March 2019, I published the scientific article in peer-reviewed journal - Ultrasound in Obstetrics & Gynaecology. The material from this article can be found in chapter 6 of my thesis. Full text available in Appendix VI.

3. "Prediction of adverse perinatal outcomes by serum placental growth factor and soluble fms-like tyrosine kinase in women undergoing induction of labour". In October 2019, I published another scientific article in peer-reviewed journal - Ultrasound in Obstetrics & Gynaecology. The material from this article can be found in chapter 7 of my thesis. Full text available in Appendix VII.

4. In 2020, I conducted a robust literature review which is included in chapter 1.

Chapter 3

MATERIAL AND METHODS

3 CHAPTER 3: MATERIAL AND METHODS

3.1 Study population

This was a prospective observational study for prediction of adverse pregnancy outcomes following IOL at Medway Maritime Hospital between May 2016 and May 2018. In my study, women booked for IOL attended the Pre-Induction Clinic within 24 hours prior to the administration of the induction agent. During the appointment, I recorded maternal characteristics, medical and obstetric history, and performed an ultrasound scan to first, determine presentation, second, estimate the fetal weight from measurements of fetal head circumference, abdominal circumference, and femur length and third, carry out transabdominal colour Doppler for measurement of UA-PI and MCA-PI. Maternal blood was obtained and stored at -80° C for subsequent biochemical analysis of PLGF and sFLT-1 (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined from the measurement of the fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.

During the study period, there were 1,902 women who underwent an IOL and met the inclusion criteria. There were 1,408 (74.0%) vaginal deliveries and 494 (26.0%) that needed caesarean section, including 47 (9.5%) for failed induction, 181 (36.6%) for failure to progress, 258 (52.2%) for fetal distress and 8 (1.6%) for other indications.

Table 3.1. Maternal and pregnancy characteristics in the study population.

Maternal and pregnancy characteristics	**Study population (n=1,902)**
Maternal age in years, median (IQR)	29.0 (25.0-33.3)
Maternal weight in kg, median (IQR)	85.0 (74.1-98.2)
Maternal height in meters, median (IQR)	1.65 (1.61-1.69)
Cigarette smoker, n (%)	252 (13.2)
Racial origin	
White, n (%)	1712 (90.0)
Black, n (%)	64 (3.4)
South Asian, n (%)	95 (5.0)
East Asian, n (%)	9 (0.5)
Mixed, n (%)	22 (1.2)
Conception	
Spontaneous, n (%)	1823 (95.8)
Assisted conception, n (%)	79 (4.2)
Obstetric history	
Nulliparous, n (%)	884 (46.5)
Parous, previous CS, n (%)	123 (6.5)
Parous, previous vaginal birth, n (%)	895 (47.1)
Medical disorders	
Chronic hypertension, n (%)	8 (0.4)
Diabetes mellitus, n (%)	150 (7.9)
Pregnancy complications	
Gestational diabetes, n (%)	127 (6.7)
Obstetric cholestasis, n (%)	87 (4.6)

Gestational hypertension, n (%)	42 (2.2)
Preeclampsia, n (%)	36 (1.9)
Amniotic fluid volume	
Normal, n (%)	1748 (91.9)
Oligohydramnios, n (%)	79 (4.2)
Polyhydramnios, n (%)	75 (3.9)
GA at delivery in weeks, median (IQR)	40.2 (39.0-41.5)
Birth weight in g, median (IQR)	3485 (3120-3850)

3.2 Study protocol

Study protocol in full can be found in Appendix I at the end of this thesis. The study flow chart is outlined below:

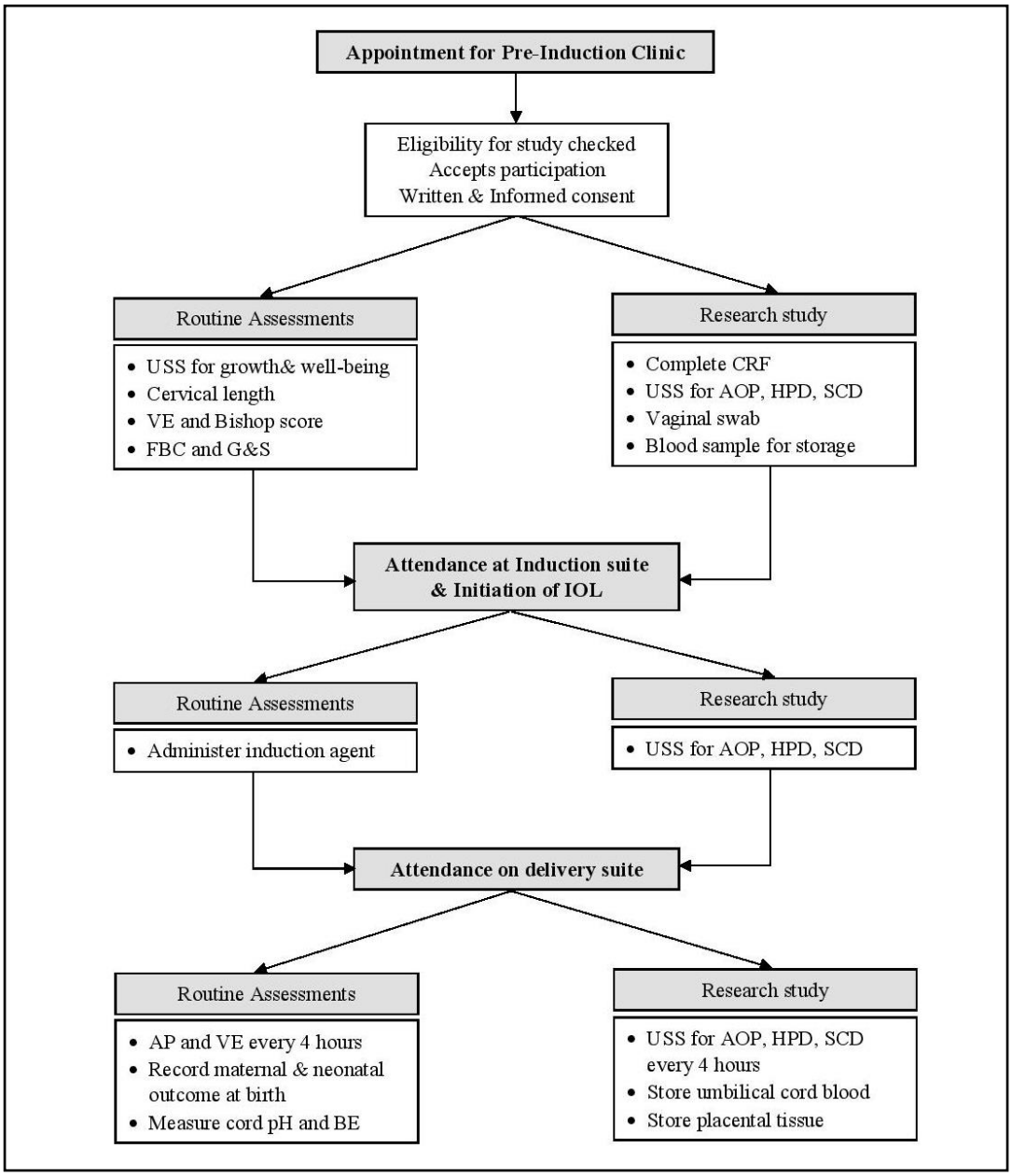


Figure 3.1 Study flow chart.

3.3 Study methods

For the conduct of this study, a Pre-Induction Clinic (PIC) was set up at Medway Maritime Hospital, where all women with singleton pregnancies booked for IOL attended for an appointment a day prior to IOL. I invited women attending the PIC to participate in the research study involving prediction of pregnancy outcomes following IOL. After obtaining informed written consent, maternal history and demographics have been recorded on an electronic clinical records form (CRF).

In the pre-induction clinic, women had a transabdominal (TA) ultrasound assessment to confirm fetal presentation, estimate fetal weight, measure amniotic fluid index, and assess fetal well-being using fetal Doppler indices. A blood sample was obtained for routine pre labour bloods as well as research bloods for PLGF and sFLT-1. They were offered a TVUS to measure cervical length and posterior cervical angle prior to digital VE to assess the Bishop Score which was performed by the midwives.

Transperineal ultrasound scan (TPUS) was performed along with the routine ultrasound assessment to check position of occiput, AOP and HPD. An additional bottle of blood was also collected and stored for future research to examine potential biomarkers of adverse outcomes. The next day, women attended the induction suite for clinical assessment.

3.4 Study objectives

The main objective of this study was to develop a model of prediction of successful IOL based on maternal factors, biophysical and biochemical markers.

During this prospective study, the study objectives evolved based on literature review, availability of new evidence, interactions with women attending the PIC and with discussion with my PhD supervisor. Hence, the study objectives were modified to include not just the initial study objectives but also include secondary research questions that were directly relevant to the original study by including the prediction of not just a successful vaginal birth but also to include prediction of adverse pregnancy outcomes as this was deemed to be equally important.

The dataset was collected in PIC over a period of two years when the study was undertaken. Subsets were derived and used for analysis in the nested studies described in this thesis. The studies examined the prediction of caesarean section for failure to progress based on maternal and pregnancy characteristics (chapter 4), cervical assessment (chapter 5), prediction of caesarean section for fetal distress as well as neonatal complications such as admission to NICU, abnormal 5-minute Apgar score and abnormal umbilical cord pH based on cerebroplacental ratio (chapter 6) and biochemical markers (chapter 7).

3.5 Study design

This was a prospective observational study in a single maternity unit in the UK.

The inclusion criteria for participants were as follows:

1. Women attending the PIC for IOL
2. Singleton pregnancies
3. Cephalic presentation
4. Informed and written consent

The exclusion criteria were as follows:

1. Multiple pregnancies
2. Women with fetal demise
3. Women less than 16 years
4. Women who were severely ill, those with learning disability, and mental illness
5. Malpresentation

Women who fulfilled the eligibility criteria received an information leaflet (Appendix III) and counselling concerning the study and those agreeing to participate were invited and requested to sign a consent form (Appendix IV).

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116).

3.6 Patient's information leaflet

Patient's information leaflet can be found in Appendix III at the end of this thesis.

3.7 Patient consent form

Patient consent form can be found in Appendix IV at the end of this thesis.

3.8 Case record form

Case record form can be found in Appendix V at the end of this thesis.

3.9 Ethical approval for study

Ethical approval for study from NHS Health Research Authority (HRA) in full can be found in Appendix II at the end of this thesis.

3.10 Recording of information

Data on pregnancy outcome were collected from the hospital maternity records. I obtained data for gestational age at delivery, mode of delivery (vaginal delivery or caesarean section), indication for caesarean section, birth weight, 5-minute Apgar score, umbilical arterial or venous pH and details of admission to neonatal intensive care unit (NICU).

3.11 Study outcomes measures

Adverse perinatal outcome was defined by the presence of any one of caesarean section for non-reassuring fetal status in labour (evidence of a non-reassuring fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1), umbilical arterial or venous cord blood pH ≤7 and ≤7.1, respectively, 5-minute Apgar score <7 or admission to NICU for ≥ 24 hours and hypoxic ischemic encephalopathy). Caesarean section for presumed fetal distress in labour was carried out if there was evidence of pathological electronic fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1. In-utero interventions were attempted based on standard local guidelines and depending on the urgency for delivery. Hypoxic-ischemic encephalopathy was diagnosed when there was disturbed neurologic function with evidence of perinatal hypoxia reflected in either a 5-minute Apgar score < 5 or umbilical artery cord pH < 7.0 or base deficit > 12 mmol/L, supported by neuroimaging evidence of acute brain injury.

3.12 Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and $\chi 2$-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics provided a significant contribution in the prediction of the adverse perinatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height were centred by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. Predicted probabilities from logistic regression analysis were used to construct receiver operating characteristic (ROC) curves to assess performance of screening for this adverse outcome.

Chapter 4

PREDICTION OF ADVERSE PERINATAL OUTCOMES BY MATERNAL FACTORS

4 CHAPTER 4: PREDICTION OF ADVERSE PERINATAL OUTCOMES BY MATERNAL FACTORS

4.1 Study introduction

Induction of labour is one of the most common obstetric procedures worldwide. Multiple professional bodies support IOL for a variety of maternal and obstetric reasons. Majority of women undergoing IOL will achieve a vaginal birth. However, a substantial proportion of women will wither have an unsuccessful IOL or will not progress in labour and hence require a caesarean section to deliver their baby.

Maternal and obstetric characteristics are known predictors of successful or failed IOL. Adequately taken history and counselling prior to IOL are vital to build a rapport with women and manage their expectations.

4.2 Study objectives

The objective of this study was to investigate the performance of prediction model for caesarean section for failure to progress by maternal characteristics including age, race, weight and high combined with maternal obstetric history obtained within 24 hours of IOL.

4.3 Study methods

4.3.1 Study population

This data for this study were derived from a prospective observational study for prediction of adverse pregnancy outcomes following IOL during the period from the 1st of May 2016 until the 31st of May 2017, at Medway Maritime Hospital. At the hospital, women booked for IOL attend the Pre-Induction Clinic within 24 hours prior to the administration of the induction agent. At this appointment, maternal characteristics as well as medical and obstetric history was recorded. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.

All singleton pregnancies that were booked for IOL at ≥ 37 weeks' gestation and delivering phenotypically normal neonates were included. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

4.3.2 Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or in vitro fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension, or preeclampsia, and obstetric history (nulliparous if no previous

pregnancies at ≥ 24 weeks and parous, with or without history of previous caesarean section). Maternal weight and height were measured.

4.3.3 Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. I obtained data for gestational age at delivery, mode of delivery (vaginal delivery or caesarean section), indication for caesarean section and birth weight. Failure to progress at 1st stage of labour was defined as labour arrest or labour dystocia at cervical dilatation between 3 and 9 centimetres despite regular uterine contractions. Failure to progress at 2nd stage was defined as lack of descent of presenting part at full cervical dilatation and maternal pushing for 1 or 2 hours. Multiparous women were allowed to push for 1 hour and nulliparous women for 2 hours, which was in line with the RCOG guidelines. Caesarean section for failure to progress was defined as abdominal delivery in cases of labour dystocia.

4.3.4 Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and $\chi 2$-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics provided a significant contribution in the prediction of caesarean section for failure to progress. Prior to the regression analysis, the continuous variables, such as age, weight and height were centred by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. Predicted probabilities from logistic regression analysis were used to construct receiver operating characteristic (ROC) curves to assess performance of screening for this adverse outcome. The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) was used for data analyses.

4.4 Study results

In the study population, there were 705 women who underwent an assessment in the PIC. There were 532 (75.5%) vaginal deliveries and 173 (24.5%) that needed an emergency caesarean section, including, 79 (45.7%) for failure to progress and 94 (54.3%) for fetal distress.

Table 4.1 Maternal and pregnancy characteristics in pregnancies with vaginal delivery compared to those that had caesarean section for failure to progress.

Maternal and pregnancy characteristics	**Vaginal delivery (n=532)**	**CS for FTP (n=79)**

Maternal age in years, median (IQR)	28.0 (24.0-32.0)	31.0 (26.0-34.0)**
Maternal weight in kg, median (IQR)	85.0 (73.6-97.5)	93.0 (82.0-107.4)**
Maternal height in meters, median (IQR)	1.66 (1.62-1.70)	1.64 (1.59-1.69)*
Cigarette smoker, n (%)	81 (15.2)	9 (11.4)
Racial origin		
White, n (%)	491 (92.3)	75 (94.9)
Black, n (%)	11 (2.1)	1 (1.3)
South Asian, n (%)	20 (3.8)	2 (2.5)
East Asian, n (%)	3 (0.6)	1 (1.3)
Mixed, n (%)	7 (1.3)	0
Conception		
Spontaneous, n (%)	522 (98.1)	74 (93.7)
Assisted conception, n (%)	10 (1.9)	5 (6.3)*
Obstetric history		
Nulliparous, n (%)	219 (41.2)	67 (84.8)**
Parous, previous CS, n (%)	21 (3.9)	5 (6.3)
Parous, previous vaginal birth, n (%)	292 (54.9)	7 (8.9)
GA at delivery in weeks, median (IQR)	39.7 (38.6-41.3)	40.6 (39.1-41.9)*
Birth weight in g, median (IQR)	3370 (2982-3740)	3600 (3350-3890)**
Birth weight $<10^{th}$ percentile, n (%)	48 (9.0)	2 (2.5)*

Significance value * $p<0.05$; ** $p<0.01$

In pregnancies that required caesarean section for fetal failure to progress, compared to those who achieved vaginal delivery, the median maternal age as well as weight were higher, and the median height was lower. Additionally, there was a significant contribution of parity in this model. Women undergoing their first ever delivery,

nulliparous women, had significantly higher risk of caesarean section for failure to progress, with OR of 12. Women aged 40, those who weighed 108kg or those who were 144cm tall, had an increased risk of failure to progress with odds ratio of 2, 2 and 5 respectively (Figure 4.1). Additionally, for every year above the age of 30, there is 12% increase in risk of caesarean section for failure to progress. Similarly, with every kg above the weight of 88, there is 4% increase in CS risk.

Univariable regression analysis demonstrated that in prediction of caesarean section for failure to progress, there was a statistically significant contribution from maternal age and weight and parous women with previous vaginal delivery. In screening for caesarean section for failure to progress by maternal factors, obstetric and medical history the DR was 67% for FPR of 20% (Figure 4.2). Addition of cervical length at transvaginal ultrasound and head to perineum distance at transperineal ultrasound improves detection rate by 5% (72%) (Figure 4.3). Parity constituted the most important predictor of successful vaginal delivery following IOL. Nulliparous women had significantly higher risk of caesarean section for failure to progress than women with a history of previous vaginal delivery, regardless of cervical length or head to perineum distance (Figure 4.4 and Figure 4.5).

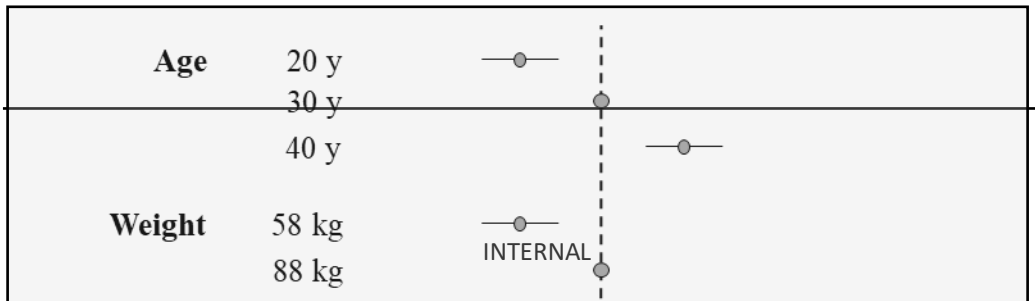


Figure 4.1 Forest plot demonstrating odds ratio for CS for failure to progress for maternal factors including age, weight, height and parity.

Table 4.2. Univariate and multivariate logistic regression analysis in prediction of caesarean section for failure to progress based on maternal and pregnancy characteristics.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	1.072 (1.030-1.117)	<0.001	1.121 (1.068-1.175)	<0.001
Maternal weight – 88 (kg)	1.022 (1.009-1.035)	<0.0001	1.039 (1.021-1.056)	<0.001
Maternal height – 1.64 (m)	0.958 (0.924-0.995)	0.025	0.910 (0.869-0.954)	<0.001
Cigarette smoker	0.706 (0.339-1.468)	0.351		
Racial origin		0.561		
White	1.000 (Reference)			
Black	0.595 (0.076-4.676)	0.622		
South Asian	0.655 (0.150-2.858)	0.573		
East Asian	2.182 (0.224-21.254)	0.502		
Mixed	-	-		
Conception				
Spontaneous	1.000 (Reference)			
Assisted conception	3.527 (1.173-10.604)	0.025		

Obstetric history		<0.0001		
Parous (reference)	1.000 (Reference)			
Nulliparous	7.980 (4.215-15.106)	<0.001	11.890 (5.951-23.755)	<0.001
Birth weight z-score	1.501 (1.173-1.921)	0.001		
GA at delivery – 40 (weeks)	1.312 (1.116-1.541)	<0.001		

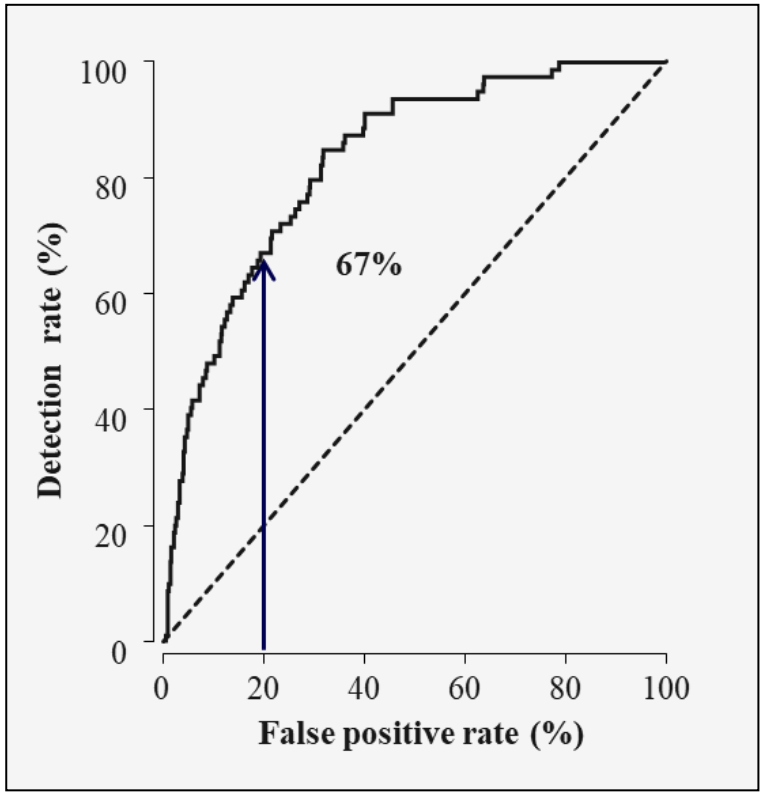


Figure 4.2 Detection rate of screening for CS for failure to progress by maternal characteristics and obstetric history

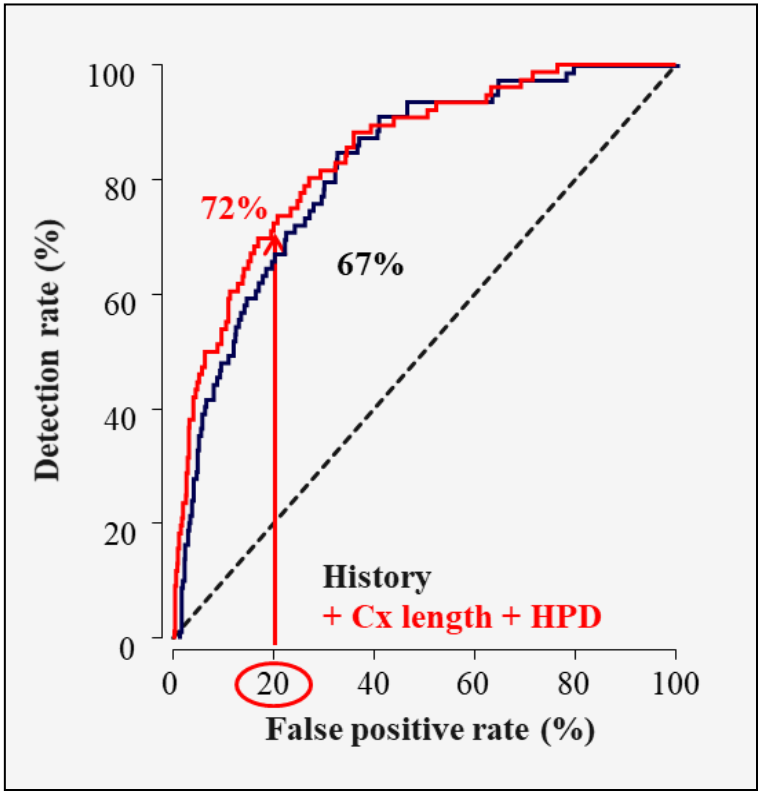


Figure 4.3 Detection rate of screening for CS for failure to progress by combined model including history, cervical length and head to perineum distance (red) compared to that from history alone (black)

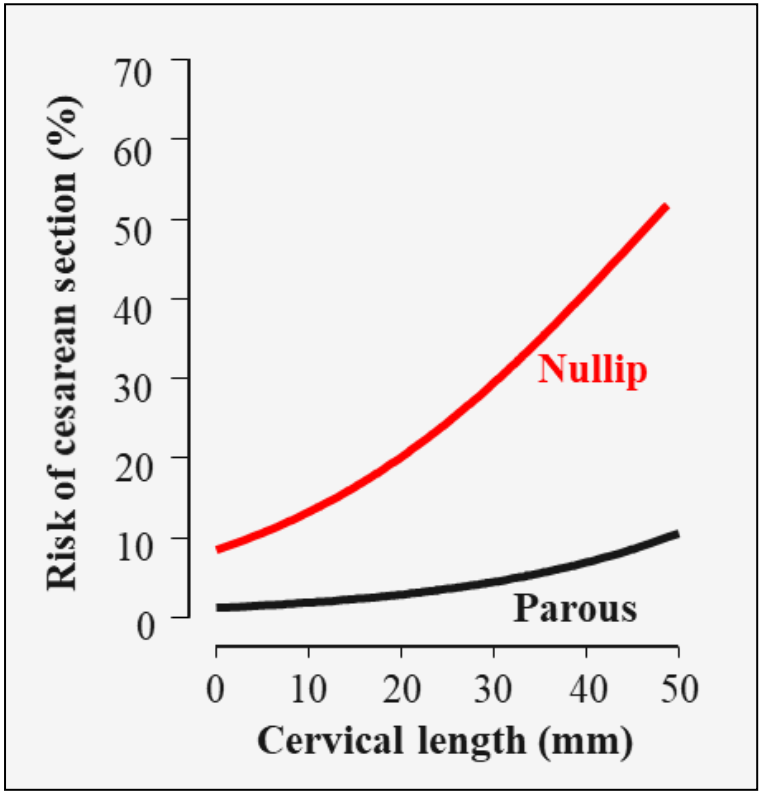


Figure 4.4 Effect of parity on risk of caesarean section for failure to progress in nulliparous (red) vs parous (black) women in relation to cervical length

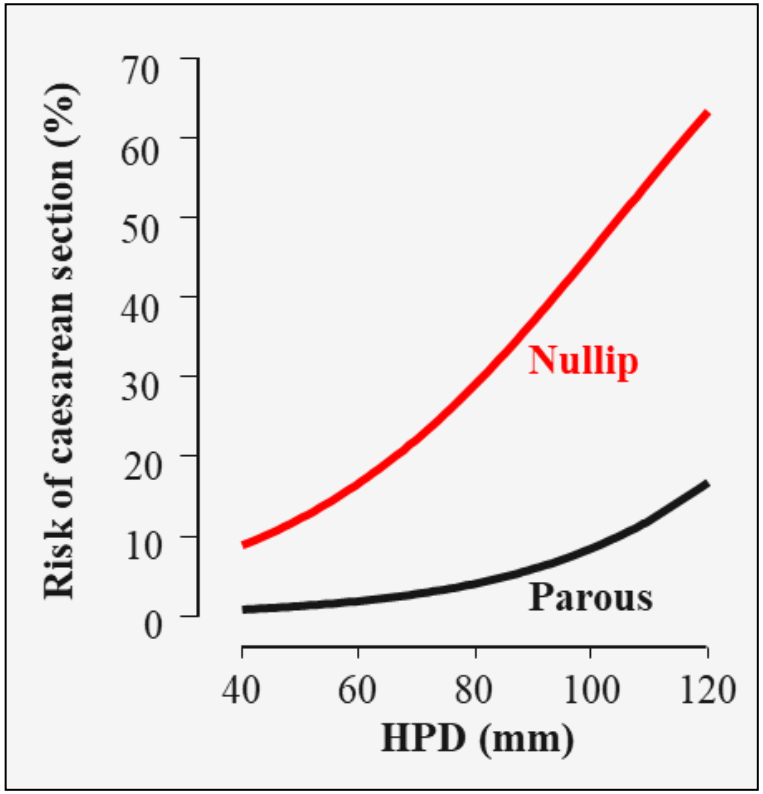


Figure 4.5 Effect of parity on risk of caesarean section for failure to progress in nulliparous (red) vs parous (black) women in relation to head to perineum distance

Chapter 5

PREDICTION OF ADVERSE PERINATAL OUTCOMES BY CERVICAL MEASUREMENTS

5 Chapter 5: PREDICTION OF ADVERSE PERINATAL OUTCOMES BY CERVICAL MEASUREMENTS

5.1 Study introduction

Approximately, 25% of women undergo induction of labour in the UK and the numbers are rising annually. Detailed maternal and obstetric history can help identify women at risk of failed IOL and those who are unlikely to progress in labour (chapter 4). Many authors have tackled the problem of predicting successful vaginal birth following induction of labour using cervical length as a predictor with DR ranging from 63% (Bueno et al, 2005) to 95% (Ware et al, 2000) for FPR of 30% and 8% respectively. Some incorporated the novel transperineal measurements of angle of progression and head to perineum distance to further improve the prediction. DR varied from 67% (Eggebo et al, 2008) to 76% (Alvarez – Colomo et al, 2015) for FPR of 47% and 15% respectively. The combination of transvaginal and transperineal scans could therefore significantly improve the prediction of failed IOL, failure to progress and a need for subsequent caesarean section.

5.2 Study objectives

The objective of this study was to investigate the performance of prediction model for caesarean section for failure to progress by transvaginal and transperineal ultrasonographic parameters such as cervical length, posterior cervical angle, cervical

compression index, angle of progression and head to perineum distance obtained within 24 hours of IOL.

5.3 Study methods

5.3.1 Study population

The data for this study were derived from a prospective observational study for prediction of adverse pregnancy outcomes following IOL in women who attended for an ultrasound scan in the pre-induction clinic at the Fetal Medicine Unit at Medway Maritime Hospital, United Kingdom. In this clinic, all women undergoing an IOL are offered an ultrasound scan to assess fetal growth and well-being prior to administration of the induction agent. The study period was from 1st of May 2016 until 31st August 2017.

Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

The inclusion criteria for this study were singleton pregnancies at or after 37 weeks' gestation, with a cephalic presentation that were booked for an IOL.

5.3.2 Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or in vitro fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension, or preeclampsia, and obstetric history (nulliparous if no previous pregnancies at ≥ 24 weeks and parous, with or without history of previous caesarean section). Maternal weight and height were measured.

5.3.3 Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal delivery or caesarean section), indication for caesarean section and birth weight. Failure to progress at 1st stage of labour was defined as labour arrest or labour dystocia at cervical dilatation between 3 and 9 centimetres despite regular uterine contractions. Failure to progress at 2nd stage was defined as lack of descent of presenting part at full cervical dilatation and maternal pushing for 1 or 2 hours depending on parity. Multiparous women were allowed to push for 1 hour and nulliparous women for 2 hours, which was in line with the RCOG guidelines. Caesarean section for failure to progress was defined as abdominal delivery in cases of labour dystocia.

5.3.4 Statistical analysis

Continuous and categorical variables were compared using Mann-Whitney U-test and χ2-square test or Fisher's exact test, respectively. The distribution of AOP was made Gaussian using logarithmic transformation (log10). Normality of distribution was assessed using probability plots and histograms. A p value of < 0.05 was considered significant and post hoc Bonferroni correction was used as necessary. In the vaginal delivery group, regression analysis was used to examine the association of AOP (Log10) with vaginal dilatation and time to delivery in active phase of labour. The area under ROC (AUROC) curves for combined model including maternal characteristics, cervical length and head to perineum distance was compared to that obtained from maternal factors alone (Figure 4.3). The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL) and Medcalc (Medcalc Software, Belgium) were used for data analyses.

5.4 Study results

In the study population, there were 1,018 women who underwent an assessment in the PIC. There were 759 (74.6%) vaginal deliveries, including 116 (15.3%) patients who had instrumental deliveries. There were 259 (25.4%) that needed an emergency caesarean section, including 60 (23.2%) for failed induction, 56 (21.6%) for failure to progress and 143 (55.2%) for fetal distress.

Table 5.1 Maternal and pregnancy characteristics in pregnancies with vaginal delivery compared to those that had caesarean section for failure to progress or a caesarean section for failed IOL Significance value * p<0.05; ** p<0.01

Maternal and pregnancy characteristics	Vaginal delivery (n=759)	CS for FTP (n=56)	CS for Failed IOL (n=60)
Maternal age in years, median (IQR)	28.0 (24.0-32.0)	29.0 (27.0-35.0)*	31.5 (25.0-34.0)*
Maternal weight in kg, median (IQR)	85.0 (74.0-97.1)	86.9 (74.5-99.8)	94.7 (82.1-107.9)**
Maternal height in meters, median (IQR)	1.65 (1.61-1.70)	1.63 (1.57-1.67)**	1.64 (1.60-1.71)
Cigarette smoker, n (%)	118 (15.5)	6 (10.7)	8 (13.3)
Racial origin			
White, n (%)	703 (92.6)	53 (94.6)	57 (95.0)
Black, n (%)	17 (2.2)	1 (1.8)	0
South Asian, n (%)	29 (3.8)	0	3 (5.0)
East Asian, n (%)	3 (0.4)	1 (1.8)	0
Mixed, n (%)	7 (0.9)	1 (1.8)	0
Conception			
Spontaneous, n (%)	741 (97.6)	55 (98.2)	55 (91.7)

Assisted conception, n (%)	18 (2.4)	1 (1.8)	5 (8.3)**
Obstetric history			
Nulliparous, n (%)	304 (40.1)	47 (83.9)**	43 (71.7)**
Parous, previous CS, n (%)			
Parous, previous vaginal birth, n (%)			
GA at delivery in weeks, median (IQR)	39.8 (38.7-41.3)	41.4 (39.9-41.9)**	40.1 (38.6-41.9)
Birth weight in g, median (IQR)	3400 (3010-3760)	3735 (3415-4115)**	3615 (3172-3940)*

Table 5.2 Univariate and multivariate logistic regression analysis in prediction of caesarean section for failure to progress based on maternal and pregnancy characteristics as well as cervical assessment.

Maternal and pregnancy characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	1.060 (1.013-1.110)	0.012	1.118 (1.059-1.180)	<0.0001
Maternal weight – 88 (kg)	1.009 (0.994-1.024)	0.253	1.023 (1.002-1.044)	0.028
Maternal height – 1.64 (m)	0.924 (0.886-0.964)	<0.0001	0.847 (0.797-0.901)	<0.0001
Cigarette smoker	0.652 (0.273-1.555)	0.335		
Racial origin		0.214		
White	1.000 (Reference)			
Black	0.780 (0.102-5.977)	0.811		
South Asian	-	-		
East Asian	4.421 (0.452-43.241)	0.201		
Mixed	1.895 (0.229-15.689)	0.553		
Conception				
Spontaneous	1.000 (Reference)			
Assisted conception	0.748 (0.098-5.712)	0.780		

Obstetric history				
Parous (reference)	1.000 (Reference)			
Nulliparous	7.816 (3.775-16.183)	<0.0001	17.725 (7.653-41.052)	<0.0001
Birth weight	1.001 (1.001-1.002)	<0.001	1.002 (1.001-1.003)	<0.0001
GA at delivery – 40 (weeks)	1.580 (1.276-1.955)	<0.001		
Cervical length	1.002 (0.973-1.032)	0.887		
Posterior cervical angle	0.992 (0.980-1.004)	0.176		
Cervical compression index	1.001 (0.976-1.026)	0.944		
Head to perineum distance	1.023 (1.006-1.041)	0.007		
Angle of progression	0.976 (0.954-0.998)	0.036		

Ultrasound measurements in prediction of caesarean section

Transvaginal USS - Cervical length, posterior cervical angle and cervical compression index

The median cervical length in vaginal deliveries was 23.0 (IQR 16.8-30.0), which was significantly lower compared to cervical length in all pregnancies who were delivered by CS (median 27.0 [IQR 19.7-33.0]; p<0.0001), those who had CS for FTP (median 28.1 [IQR 20.6-33.6]; p<0.0001), and CS for failed induction (median 29.7 [IQR 25.0-35.0]; p<0.0001) (Figure 5.1). Similarly, the posterior cervical angle was significantly lower in pregnancies delivering by CS for any indication (median 93 [IQR 76-112]; p<0.0001), those who had CS for FTP (median 88 [IQR 72-109]; p<0.0001) and those who had CS for failed induction (median 81 [IQR 68-97]; p<0.0001) compared to those who had vaginal deliveries (median 100 [IQR 85-116]) (Figure 5.2). Compared to those who had vaginal deliveries (median 63.6 [IQR 54.4-71.9]), the cervical compression index was significantly higher in pregnancies that required CS for failed induction (median 66.7 [IQR 61.6-75.6]; p=0.009) but not in those that had CS for any indication (p=0.05) or those who had CS for FTP (p=0.05). (Table 5.1) (Figure 5.3)

Study group	Cervical length	Posterior cervical angle	Cervical compression index
Vaginal	23.0 (16.5-30.0)	100.0 (85.0-116.3)	63.6 (54.4-71.9)
All CS	26.8 (19.6-33.0) ***	93.5 (76.0-112.0) **	65.5 (57.7-73.0)
All FTP	28.0 (20.3-33.6) ***	88.5 (73.0-109.8) ***	66.7 (59.1-75.0)
Failed IOL	29.7 (25.0-35.0) ***	81.0 (70.0-99.0) ***	67.6 (61.6-75.6)

Table 5.3 Prediction of mode of delivery by transvaginal ultrasound scan including cervical length, posterior cervical angle and cervical compression index. Significance value: * p<0.01; ** p<0.001; *** p<0.0001

Transperineal USS – Angle of progression and head to perineum distance

The median AOP in vaginal deliveries was 101 (IQR 93-110), which was significantly different compared to AOP in all pregnancies who were delivered by CS (median 98 [IQR 90-106]; p<0.0001), those who had CS for FTP (median 97 [IQR 90-106]; p<0.0001), and CS for failed induction (median 96 [IQR 87-104]; p<0.0001) (Figure 5.5). Similarly, the HPD was significantly higher in pregnancies delivering by CS for any indication (median 76 [IQR 67-91]; p<0.0001), those who had CS for FTP (median 78 [IQR 70-91]; p<0.0001) and those who had CS for failed induction (median 81 [IQR 70-92]; p<0.0001) compared to those who had vaginal deliveries (median 71 [IQR 62-82]; p<0.0001). (Table 5.2) (Figure 5.6).

Study group	HPD (mm)	AOP (mm)
Vaginal	71 (62-82)	101 (93-110)
All CS	76 (67-91) ***	98 (90-106) ***
All FTP	78 (70-91) ***	97 (90-106) **
Failed IOL	81 (70-92) ***	96 (87-104) **

Table 5.4 Prediction of mode of delivery by transperineal ultrasound scan including head to perineum distance and angle of progression. Significance value: * $p<0.01$; ** $p<0.001$; *** $p<0.0001$

In pregnancies with vaginal delivery, there was a linear association between cervical length and induction to delivery interval: Induction to delivery interval = 5.875 + (0.636 x cervical length); $R2=0.129$; $p<0.0001$. (Figure 5.4).

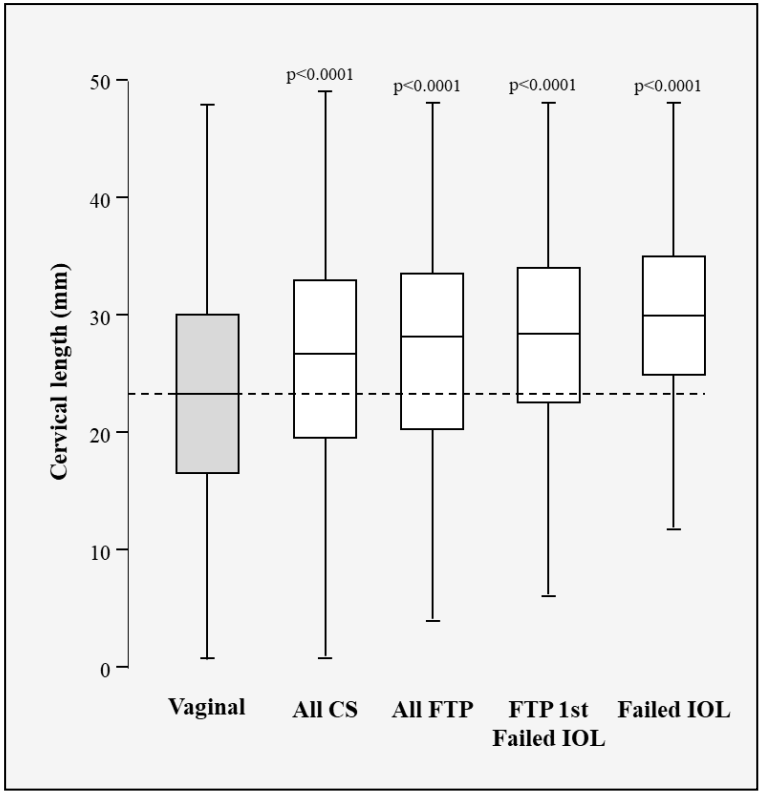


Figure 5.1 Box and whisker plot illustrating impact of cervical length on mode of delivery

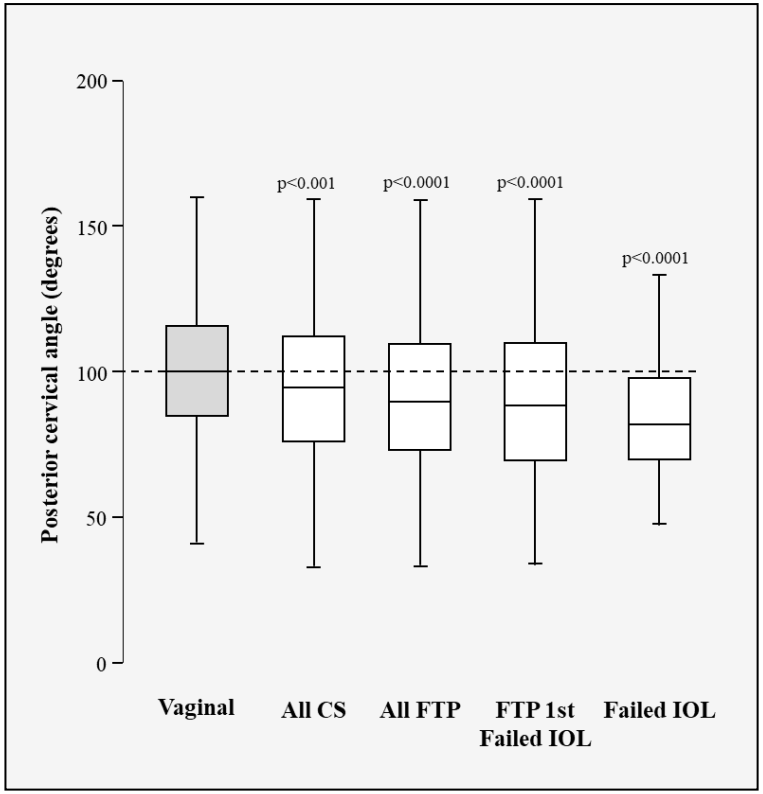


Figure 5.2 Box and whisker plot illustrating impact of posterior cervical angle on mode of delivery

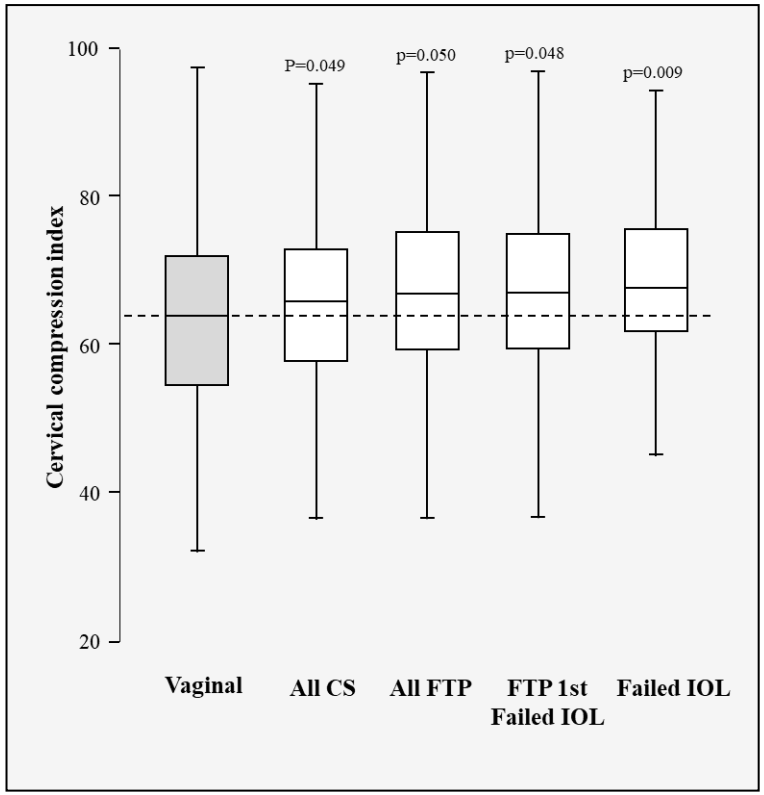


Figure 5.3 Box and whisker plot illustrating impact of cervical compression index on mode of delivery

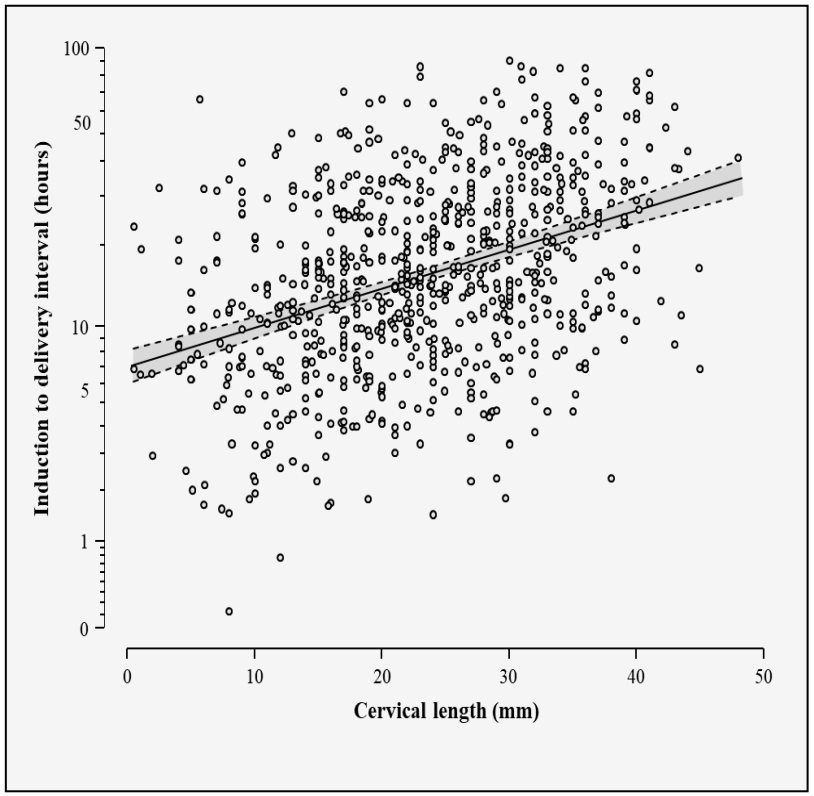


Figure 5.4 Relationship between cervical length measurement and induction to delivery interval

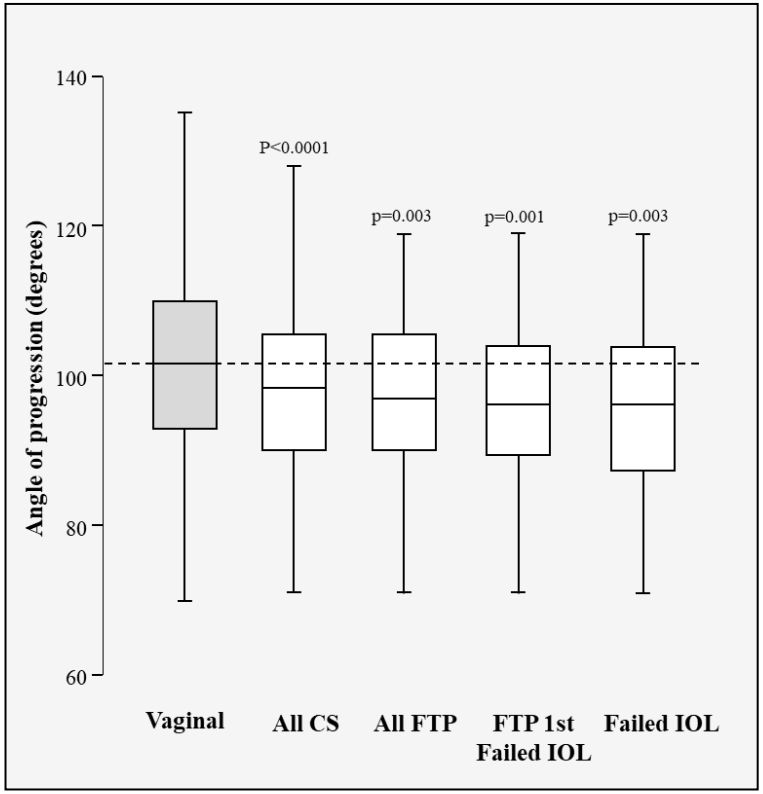


Figure 5.5 Box and whisker plot illustrating impact of cervical compression index on mode of delivery

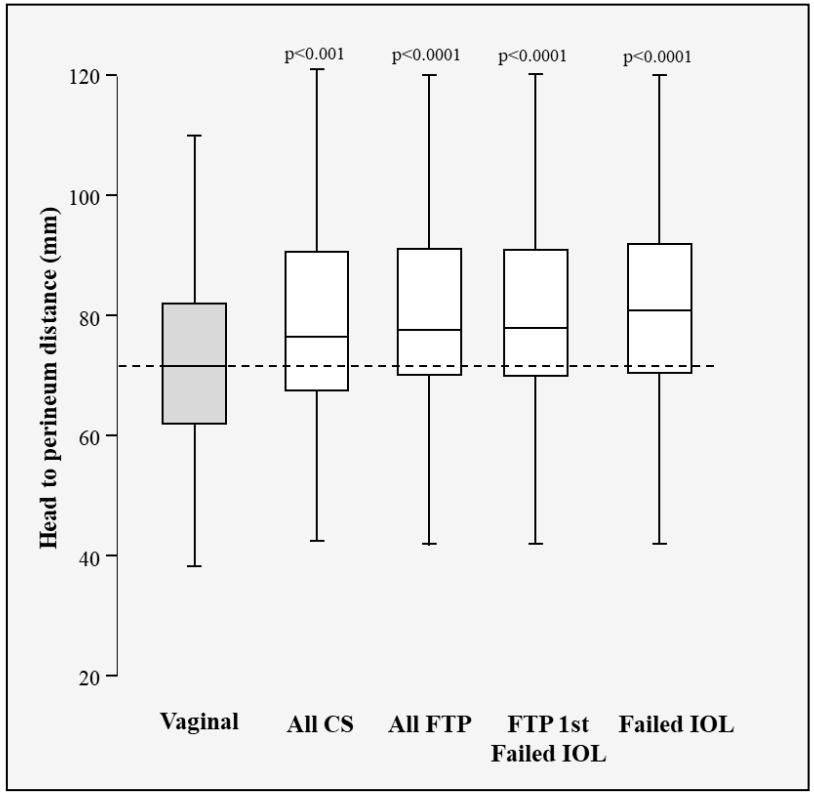


Figure 5.6 Box and whisker plot illustrating impact of head to perineum distance on mode of delivery

Chapter 6

PREDICTION OF ADVERSE PERINATAL OUTCOMES BY THE CEREBROPLACENTAL RATIO

6 Chapter 6: PREDICTION OF ADVERSE PERINATAL OUTCOMES BY THE CEREBROPLACENTAL RATIO

6.1 Study introduction

Doppler assessment of impedance to flow in the umbilical artery (UA), fetal middle cerebral artery (MCA) and the ratio of the pulsatility index (PI) in these vessels, or cerebroplacental ratio (CPR), are used for assessment of fetal oxygenation. In the 1980's studies of fetal blood obtained by cordocentesis from small for gestational age (SGA) fetuses demonstrated that increased impedance to flow in the UA and decreased impedance to flow in MCA are associated with fetal hypoxemia and acidaemia. Subsequent studies in SGA fetuses in the 1990's reported that low CPR was associated with adverse perinatal outcome, including higher rates of perinatal death, caesarean section for fetal distress in labour, neonatal acidosis, 5-minute Apgar scores <7, and neonatal intensive care unit (NICU) stay >24 hours. Renewed interest in the CPR has been stimulated by the possibility that this index may be predictive of adverse perinatal outcome not only in SGA but also in appropriately grown for gestational age (AGA) fetuses. Prior et al, measured the CPR in 400 pregnancies with AGA fetuses immediately before established labour and reported that CPR <10th percentile, compared to those with CPR ≥10th percentile, was associated with a 6-fold increased risk for delivery by caesarean section for fetal distress and that in the group with CPR >90th percentile none had caesarean section for fetal distress. Subsequent studies proposed that a low CPR can identify AGA fetuses that have not reached their growth

potential as a consequence of suboptimal placental function and that low CPR, measured within two weeks of birth, is associated with the need for operative delivery for presumed fetal compromise and with neonatal unit admission at term regardless of the fetal size. However, these studies examined high-risk pregnancies and did not report on the performance of CPR in the prediction of adverse outcome.

A screening study in 30,870 women with singleton pregnancies attending for a routine hospital visit at 30-34 weeks' gestation investigated the potential value of CPR in the prediction of adverse perinatal outcome and reported that although there was an association between CPR and birthweight Z-score, umbilical cord blood pH and admission to NICU, the performance of screening by CPR was poor with detection rates (DR) of 5-11% at a false positive rate (FPR) of 5%. A possible explanation for such poor performance of screening was that the perinatal adverse events at term were too remote from the gestation at which CPR was assessed. Another study of 6,178 pregnancies routinely screened at 35-37 weeks' gestation, also reported significant associations between CPR and indicators of adverse perinatal outcome but again the performance of screening by CPR was poor with DR of 6-15%, at FPR of 6%.

6.2 Study objectives

The objective of this study was to investigate whether the performance of screening by CPR for adverse perinatal outcome was improved by undertaking the assessment within 24 hours of IOL.

6.3 Study methods

6.3.1 Study population

The data for this study were derived from a prospective observational study for prediction of adverse pregnancy outcomes following IOL during the period 1st May 2016 to 31st July 2018, at Medway Maritime Hospital, England. At our hospital, women booked for IOL attend the Pre-Induction Clinic within 24 hours prior to the administration of the induction agent. We recorded maternal characteristics, medical and obstetric history, and performed an ultrasound scan to first, determine presentation, second, estimate the fetal weight from measurements of fetal head circumference, abdominal circumference, and femur length, third, assess amniotic fluid volume by measurement of deepest pool of fluid without any fetal parts and classifying oligohydramnios and polyhydramnios by a deepest pool of < 2 cm and > 8 cm, respectively, and fourth, to carry out transabdominal colour Doppler for measurement of the PI in the UA and MCA. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.

We included singleton pregnancies that were booked for IOL at ≥ 37 weeks' gestation and delivering phenotypically normal neonates. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

6.3.2 Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or in vitro fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension, or preeclampsia, and obstetric history (nulliparous if no previous pregnancies at ≥ 24 weeks and parous, with or without history of previous caesarean section). Maternal weight and height were measured.

The indications for IOL were postdates (n=710), maternal request (n=278), diabetes mellitus or gestational diabetes (n=150), obstetric cholestasis (n=86), chronic hypertension, preeclampsia or gestational hypertension (n=84), suspected SGA fetus (n=197), reduced fetal movements (n=180), suspected large for gestational age fetus (n=72), spontaneous prelabour amniorrhexis (n=98), polyhydramnios (n=31), maternal medical condition such cardiac disease (n=12), or antepartum haemorrhage (n=4).

6.3.3 Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal delivery or

caesarean section), indication for caesarean section, birth weight, 5-minute Apgar score, umbilical arterial or venous pH and details of admission to neonatal intensive care unit (NICU). Adverse outcome was defined as first, caesarean section for presumed fetal distress in labour and second, adverse neonatal outcome (umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-minute Apgar score <7, admission to the NICU for > 24 hours and hypoxic ischemic encephalopathy). Caesarean section for presumed fetal distress in labour was carried out if there was evidence of a pathological electronic fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1. In-utero interventions were attempted based on standard local guidelines and depending on the urgency for delivery. Hypoxic ischemic encephalopathy was diagnosed when there was disturbed neurologic function with evidence of perinatal hypoxia reflected in either a 5-minute Apgar score < 5 or umbilical artery cord pH < 7.0 or base deficit > 12 mmol/L, supported by neuroimaging evidence of acute brain injury.

6.3.4 Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and $\chi 2$-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics and measurements of fetoplacental Dopplers, provided a significant contribution in the prediction of caesarean section for fetal distress and adverse neonatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height were centred by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA PI and MCA PI and their ratio were converted to multiples of the median (MoM) after adjustment for gestational age. The birth weight Z-score was derived from the normal range for gestational age. We estimated cut-offs for 5th, 10th, 90th and 95th percentiles for UA PI, MCA PI, and CPR and determined the prevalence of abnormal Doppler values in each of the outcome groups. We examined the performance of CPR MoM in the sub-groups of SGA fetuses (birthweight <10th percentile) and non-SGA fetuses (birthweight ≥10th percentile). Predicted probabilities from logistic regression analysis were used to construct receiver operating characteristic (ROC) curves to assess performance of screening for these adverse outcomes. The area under ROC (AUROC) curves for fetal Doppler alone was compared to that obtained from all factors.

The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) was used for data analyses.

6.4 Study results

Table 6.1. Maternal and pregnancy characteristics in pregnancies with vaginal delivery compared to those that had caesarean section for fetal distress.

Maternal and pregnancy characteristics	Vaginal delivery (n=1,408)	CS for FD (n=258)
Maternal age in years, median (IQR)	28.7 (24.8-33.1)	29.8 (25.8-33.6)*
Maternal weight in kg, median (IQR)	83.8 (73.0-96.4)	88.2 (77.0-102.3)**
Maternal height in meters, median (IQR)	1.65 (1.61-1.70)	1.65 (1.60-1.68)
Cigarette smoker, n (%)	200 (14.2)	27 (10.5)
Racial origin		
White, n (%)	1283 (91.1)	217 (84.1)
Black, n (%)	41 (2.9)	14 (5.4)*
South Asian, n (%)	61 (4.3)	20 (7.8)*
East Asian, n (%)	7 (0.5)	1 (0.4)
Mixed, n (%)	16 (1.1)	6 (2.3)
Conception		
Spontaneous, n (%)	1361 (96.7)	243 (94.2)
Assisted conception, n (%)	47 (3.3)	15 (5.8)
Obstetric history		
Nulliparous, n (%)	545 (38.7)	175 (67.8)
Parous, previous CS, n (%)	61 (4.3)	27 (10.5)**
Parous, previous vaginal birth, n (%)	802 (57.0)	56 (21.7)**
Medical disorders		
Chronic hypertension, n (%)	7 (0.5)	1 (0.4)
Diabetes mellitus, n (%)	15 (1.1)	3 (1.2)
Pregnancy complications		

Gestational diabetes, n (%)	87 (6.2)	21 (8.1)
Obstetric cholestasis, n (%)	69 (4.9)	9 (3.5)
Gestational hypertension, n (%)	33 (2.3)	5 (1.9)
Preeclampsia, n (%)	17 (1.2)	10 (3.9)**
Amniotic fluid volume		
Normal, n (%)	1320 (93.8)	221 (85.7)
Oligohydramnios, n (%)	47 (3.3)	22 (8.5)**
Polyhydramnios, n (%)	41 (2.9)	15 (5.8)*
Fetal-placental Doppler		
UA PI in MoM, median (IQR)	1.03 (0.91-1.16)	1.06 (0.92-1.20) *
UAPI >90th percentile, n (%)	269 (19.1)	64 (24.8) *
MCA PI in MoM, median (IQR)	0.98 (0.85-1.14)	0.97 (0.82-1.09)
MCAPI <10th percentile, n (%)	274 (19.5)	64 (24.8) *
CPR in MoM, median (IQR)	0.95 (0.80-1.13)	0.90 (0.74-1.10) **
CPR<10th percentile, n (%)	310 (22.0)	76 (29.5) **
GA at delivery in weeks, median (IQR)	40.1 (39.0-41.5)	40.5 (39.4-41.6)**
Birth weight in g, median (IQR)	3460 (3087-3800)	3530 (3100-3873)
Birth weight <10th percentile, n (%)	264 (18.8)	55 (21.3)
Neonatal morbidity		
5 minute Apgar score <7, n (%)	6 (0.4)	10 (3.9)**
Low cord blood pH [a], n (%)	30 (2.1)	9 (3.5)
Admission to NICU for >24 hours, n (%)	20 (1.4)	18 (7.0)**
Hypoxic ischemic encephalopathy, n (%)	0	1 (0.4)

Significance value * p<0.05; ** p<0.01

Table 6.2. Maternal and pregnancy characteristics in pregnancies with adverse neonatal outcome compared to those without.

Maternal and pregnancy characteristics	**No Adverse neonatal outcome (n=1,819)**	**Adverse neonatal outcome (n=71)**
Maternal age in years, median (IQR)	29.1 (25.0-33.3)	28.7 (25.2-32.8)
Maternal weight in kg, median (IQR)	85.0 (74.2-98.2)	86.0 (72.3-98.0)
Maternal height meters, median (IQR)	1.65 (1.61-1.69)	1.65 (1.61-1.69)
Cigarette smoker, n (%)	243 (13.4)	9 (12.7)
Racial origin		
Caucasian, n (%)	1,640 (90.2)	63 (88.7)
Afro-Caribbean, n (%)	60 (3.3)	3 (4.2)
South Asian, n (%)	88 (4.8)	5 (7.0)
East Asian, n (%)	9 (0.5)	0
Mixed, n (%)	22 (1.2)	0
Conception		
Spontaneous, n (%)	1,745 (95.9)	67 (94.4)
Assisted conception, n (%)	74 (4.1)	4 (5.6)
Obstetric history		
Nulliparous, n (%)	834 (45.8)	44 (62.0)
Parous, previous CS, n (%)	117 (6.4)	5 (7.0)
Parous, previous vaginal birth, n (%)	868 (47.7)	22 (31.0)**
Medical disorders		
Chronic hypertension, n (%)	8 (0.4)	0
Diabetes mellitus, n (%)	21 (1.2)	1 (1.4)
Pregnancy complications		
Gestational diabetes, n (%)	123 (6.8)	4 (5.6)

Obstetric cholestasis, n (%)	84 (4.6)	3 (4.2)
Gestational hypertension, n (%)	39 (2.1)	3 (4.2)
Preeclampsia, n (%)	35 (1.9)	1 (1.4)
Amniotic fluid volume		
Normal, n (%)	1,673 (92.0)	63 (88.7)
Oligohydramnios, n (%)	74 (4.1)	5 (7.0)
Polyhydramnios, n (%)	72 (4.0)	3 (4.2)
Fetal-placental Doppler		
UA PI in MoM, median (IQR)	1.03 (0.91-1.16)	1.07 (0.93-1.19)
UA PI >90th percentile, n (%)	354 (19.5)	15 (21.1)
MCA PI in MoM, median (IQR)	0.98 (0.84-1.12)	0.92 (0.80-1.04)*
MCA PI <10th percentile, n (%)	362 (19.9)	20 (28.2)
CPR in MoM, median (IQR)	0.95 (0.79-1.13)	0.87 (0.71-1.07)**
CPR <10th percentile, n (%)	407 (22.4)	24 (33.8)*
GA at delivery in weeks, median (IQR)	40.2 (39.0-41.5)	40.3 (39.2-41.5)
Birth weight in g, median (IQR)	3490 (3120-3850)	3390 (3010-3775)
Birth weight <10th percentile, n (%)	325 (17.9)	16 (22.5)
Neonatal morbidity		
5 minute Apgar score <7, n (%)	-	19 (26.8)
Low cord blood pH [a], n (%)	-	42 (59.2)
Admission to NICU for >24 hr, n (%)	-	28 (39.4)
HIE, n (%)	-	1 (1.4)

IQR: interquartile range; UA: umbilical artery; MCA: Middle cerebral artery; CPR: Cerebroplacental ratio; NICU: Neonatal intensive care unit; HIE: Hypoxic ischaemic encephalopathy Significance value* $p<0.05$; ** $p<0.01$.

6.4.1 Caesarean section for fetal distress

The maternal and pregnancy characteristics of those delivering by caesarean section for fetal distress are compared to those with vaginal delivery in Table 6.1. In pregnancies that required caesarean section for fetal distress, compared to those delivering vaginally, the median maternal age and weight were higher, there was a higher incidence of women of Black and South Asian racial origin, parous women with a previous caesarean section, PE, oligohydramnios and polyhydramnios and, higher median gestational age at delivery and UA PI MoM and lower CPR MoM, higher prevalence of UA PI MoM >90th percentile and CPR MoM <10th percentile.

Univariable regression analysis demonstrated that in prediction of caesarean section for fetal distress, there was a statistically significant contribution from maternal age and weight, Black and South Asian racial origin, parous women with previous vaginal delivery, PE, gestational age at delivery, amniotic fluid volume, UA PI MoM and CPR MoM (Table 6.3). Multivariable regression analysis demonstrated that in prediction of caesarean section for fetal distress, there was a statistically significant contribution from all above factors except UA PI MoM ($p=0.264$) ($R2=0.209$; $p<0.0001$) (Table 5.3).

In screening for caesarean section for fetal distress by maternal factors, obstetric and medical history the DR was 39.1% at FPR of 10%; addition of CPR did not improve the performance of screening (AUROC: 0.767, 95% CI 0.733, 0.800 vs. 0.763, 95%

CI 0.730, 0.796; p=0.271) In SGA neonates, the performance of screening by maternal factors, obstetric and medical history (DR 30.9%, FPR 10%) was improved by the addition of CPR (DR 34.5%, FPR 10%; AUROC: 0.658, 95% CI 0.604, 0.710 vs. 0.672, 95% CI 0.617, 0.723; p=0.048).

The CPR was <10th percentile in 50.9% (28 of 55) of SGA neonates that were delivered by caesarean section for fetal distress and in 29.9% (79 of 264) of SGA neonates that were born vaginally (p=0.003). In the non-SGA neonates, the CPR was <10th percentile in 23.6% (48 of 203) of those delivered by caesarean section for fetal distress and in 20.2% (231 of 1,144) of those that were born vaginally (p=0.263).

6.4.2 Adverse neonatal outcome

The maternal and pregnancy characteristics of those with adverse neonatal outcome are compared to those without such outcome in Table 6.2. In pregnancies with adverse neonatal outcome, compared to those without, there was a lower incidence of parous women with previous vaginal birth, lower median MCA PI MoM and CPR MoM, and higher prevalence of CPR MoM <10th percentile.

Univariable regression analysis demonstrated that in prediction of adverse neonatal outcome, there was a statistically significant contribution from parity, MCA PI MoM and CPR MoM (Table 6.4). Multivariable regression analysis demonstrated that in prediction of adverse neonatal outcome there was a statistically significant

contribution from parous women with a previous vaginal birth and CPR MoM but not MCA PI MoM (p=0.522) (R2=0.025; p=0.001) (Table 6.4). The performance of screening by history alone in prediction of adverse neonatal outcome (DR 12.8% at FPR of 10%) was significantly improved by the addition of CPR (DR 16.9% at FPR of 10%; AUROC: 0.581, 95% CI 0.514, 0.647 vs. 0.632, 95% CI 0.573, 0.692; p=0.028).

The CPR was <10th percentile in 31.3% (5 of 16) of SGA neonates with adverse neonatal outcome and in 34.2% (111 of 325) of SGA neonates without such adverse outcome (p=0.811). In the non-SGA neonates, the CPR was <10th percentile in 34.5% (19 of 55) of those with adverse neonatal outcome and in 19.8% (296 of 1,494) of those without adverse outcome (p=0.008).

Table 6.3. Univariate and multivariate logistic regression analysis in prediction of caesarean section for fetal distress

Maternal and pregnancycharacteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	1.026 (1.004-1.050)	0.023	1.065 (1.038-1.093)	<0.0001
Maternal weight – 88 (kg)	1.014 (1.007-1.021)	<0.0001	1.022 (1.013-1.031)	<0.0001
Maternal height – 1.64 (m)	0.986 (0.965-1.007)	0.202	0.956 (0.932-0.981)	0.001
Cigarette smoker	0.706 (0.461-1.081)	0.109		
Racial origin		0.014		
White	1.000 (Reference)			
Black	2.019 (1.082-3.766)	0.027	2.444 (1.212-4.929)	0.013
South Asian	1.939 (1.147-3.277)	0.013	1.970 (1.092-3.552)	0.024
East Asian	0.845 (0.103-6.899)	0.875		
Mixed	2.217 (0.858-5.729)	0.100		
Conception				
Spontaneous	1.000 (Reference)			
Assisted conception	1.787 (0.984-3.247)	0.057		
Obstetric history				
Nulliparous	1.000 (Reference)			
Parous, previous CS	1.378 (0.850-2.237)	0.194		

Parous, previous VD	0.217 (0.158-0.299)	<0.0001	0.167 (0.118-0.236)	<0.0001
Medical disorders				
Chronic hypertension	0.779 (0.095-6.356)	0.815		
Pre-existing DM	1.093 (0.314-3.801)	0.889		
Pregnancy complications				
Gestational diabetes	1.345 (0.819-2.210)	0.241		
Obstetric cholestasis	0.701 (0.346-1.423)	0.326		
Gestational hypertension	0.823 (0.318-2.219)	0.689		
Preeclampsia	3.299 (1.493-7.289)	0.003	3.102 (1.288-7.467)	0.006
Amniotic fluid volume		<0.0001		<0.0001
Normal	1.000 (Reference)			
Oligohydramnios	2.796 (1.652-4.731)	<0.0001	2.476 (1.381-4.441)	0.002
Polyhydramnios	2.185 (1.189-4.015)	0.012	3.443 (1.753-6.762)	<0.0001
Fetal-placental Doppler				
UA PI MoM	2.664 (1.386-5.122)	0.003		
MCA PI MoM	0.569 (0.288-1.125)	0.105		
Cerebroplacental ratio MoM	0.453 (0.262-0.781)	0.004	0.454 (0.249-0.828)	0.010
Birth weight z-score	0.987 (0.897-1.085)	0.782		
GA at delivery – 40 (weeks)	1.179 (1.071-1.298)	0.001	1.166 (1.046-1.300)	0.006

Table 6.4. Univariate and multivariate logistic regression analysis in prediction of adverse neonatal outcome

Maternal and pregnancycharacteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	0.996 (0.956-1.036)	0.830		
Maternal weight – 88 (kg)	1.000 (0.988-1.013)	0.965		
Maternal height – 1.64 (m)	0.985 (0.949-1.023)	0.439		
Cigarette smoker	0.941 (0.462-1.919)	0.868		
Racial origin				
White	1.000 (Reference)			
Black	1.302 (0.397-4.264)	0.663		
South Asian	1.479 (0.580-3.770)	0.412		
East Asian	-	-		
Mixed	-	-		
Conception				
Spontaneous	1.000 (Reference)			
Assisted conception	1.408 (0.500-3.964)	0.517		
Obstetric history		0.022		
Nulliparous	1.000 (Reference)			
Parous, previous CS	0.810 (0.315-2.084)	0.662		

Parous, previous VD	0.480 (0.285-0.808)	0.006	0.550 (0.344-0.880)	0.013
Medical disorders				
Chronic hypertension	-	-		
Pre-existing DM	1.223 (0.162-9.223)	0.845		
Pregnancy complications				
Gestational diabetes	0.823 (0.295-2.295)	0.710		
Obstetric cholestasis	0.911 (0.281-2.956)	0.877		
Gestational hypertension	2.014 (0.607-6.679)	0.253		
Preeclampsia	0.728 (0.098-5.392)	0.756		
Amniotic fluid volume				
Normal	1.000 (Reference)			
Oligohydramnios	1.794 (0.701-4.593)	0.223		
Polyhydramnios	1.106 (0.339-3.608)	0.867		
Fetal-placental Doppler				
UA PI MoM	2.831 (0.909-8.816)	0.073		
MCA PI MoM	0.250 (0.077-0.813)	0.021		
Cerebroplacental ratio MoM	0.278 (0.108-0.714)	0.008	0.301 (0.117-0.773)	0.008
Birth weight z-score	0.869 (0.738-1.024)	0.094		
GA at delivery – 40 (weeks)	0.967 (0.822-1.137)	0.686		

Chapter 7

PREDICTION OF ADVERSE PERINEAL OUTCOMES BY SERUM PLACENTAL GROWTH FACTOR AND SOLUBLE FMS-LIKE THYROSINE KINASE

7 Chapter 7: PREDICTION OF ADVERSE PERINATAL OUTCOMES BY SERUM PLACENTAL GROWTH FACTOR AND SOLUBLE FMS-LIKE THYROSINE KINASE

7.1 Study introduction

In women at term impaired placentation and fetal hypoxemia, reflected in low serum levels of the angiogenic placental growth factor (PLGF), high levels of the antiangiogenic soluble fms–like tyrosine kinase 1 (sFLT-1) and reduced cerebroplacental ratio (CPR), are associated with increased risk of adverse perinatal outcome in both small for gestational age (SGA) and non-SGA babies.

Such associations raised the possibility that serum biomarkers of impaired placentation could provide clinically useful information in the prediction and prevention of adverse perinatal outcome. However, the studies reported contradictory results concerning the performance of biomarkers for prediction of adverse outcome, which could at least in part be attributed to different intervals between assessment and delivery. In order to overcome this problem I decided to investigate the potential value of biomarkers measured within 24 hours of IOL at term. In a previous study of 1,902 women with singleton pregnancies undergoing IOL at ≥ 37 weeks' gestation, I found that low CPR was associated with increased risk of caesarean section for non-reassuring fetal status in labour and adverse neonatal outcome, but the performance of CPR for such surrogates of adverse perinatal outcome was poor.

7.2 Study objectives

The objective of this study is to investigate the additive value of serum PLGF and sFLT-1, measured within 24 hours of IOL, on the performance of screening for adverse perinatal outcome provided by maternal risk factors and CPR.

7.3 Study methods

7.3.1 Study population

This was a prospective observational study for prediction of adverse pregnancy outcomes following IOL at Medway Maritime Hospital, between July 2016 and August 2017. In this hospital, women booked for IOL attend the Pre-Induction Clinic within 24 hours prior to the administration of the induction agent. At this appointment, we recorded maternal characteristics, medical and obstetric history, and performed an ultrasound scan to first, determine presentation, second, estimate the fetal weight from measurements of fetal head circumference, abdominal circumference, and femur length and third, carry out transabdominal colour Doppler for measurement of UA-PI and MCA-PI. Maternal blood was obtained and stored at -80°C for subsequent biochemical analysis of PLGF and sFLT-1 (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined from the measurement of the

fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.

We included singleton pregnancies that were booked for IOL at ≥ 37 weeks' gestation and delivering phenotypically normal neonates for whom there were available measurements of maternal serum PLGF and sFLT-1. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

7.3.2 Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or in vitro fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension, or preeclampsia, and obstetric history (nulliparous if no previous pregnancies at ≥ 24 weeks and parous, with or without history of previous caesarean section). Maternal weight and height were measured and body mass index (BMI) was calculated.

7.3.3 Indications for induction of labour

The indications for IOL were postdates (n=256), maternal request (n=94), diabetes mellitus or gestational diabetes (n=74), obstetric cholestasis (n=41), chronic hypertension, preeclampsia or gestational hypertension (n=33), suspected SGA fetus (n=106), reduced fetal movements (n=88), suspected large for gestational age fetus (n=31), spontaneous prelabour amniorrhexis (n=42), polyhydramnios (n=16), maternal medical condition such cardiac disease (n=11), or antepartum haemorrhage (n=3).

7.3.4 Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal delivery or caesarean section), indication for caesarean section, birth weight, 5-minute Apgar score, umbilical arterial or venous pH and details of admission to neonatal intensive care unit (NICU).

Adverse perinatal outcome was defined by the presence of any one of caesarean section for non-reassuring fetal status in labour (evidence of a non-reassuring fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1), umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-minute Apgar score < 7 or admission to NICU for ≥ 24 hours.

7.3.5 Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and $\chi 2$-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%. Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics, measurements of fetal-placental Dopplers and maternal serum PLGF and sFLT-1, provided a significant contribution in the prediction of adverse perinatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height were centred by subtracting the arithmetic mean from each value. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA PI, MCAPI and their ratio (CPR) were converted to multiples of the median (MoM) after adjustment for gestational age and the measured PLGF and sFLT-1 were converted to MoM after adjustment for gestational age, maternal characteristics and machine used for the assays. The birth weight Z-score was derived from the normal range for gestational age. We estimated cut- offs for 10th and 90th percentiles for UA-PI, MCA-PI, CPR, PLGF and sFLT-1 and determined the prevalence of abnormal biomarker values in the outcome groups. Predicted probabilities from logistic regression analysis were used to construct receiver operating characteristic (ROC) curves to assess performance of screening for adverse perinatal outcome.

The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) was used for data analyses.

7.4 Study results

7.4.1 Study population

During the study period, there were 795 women undergoing IOL who met the inclusion criteria. There were 653 (82.1%) pregnancies without and 142 (17.9%) with adverse perinatal outcome, including 114 (80.3%) with emergency caesarean section for non-reassuring fetal status in labour and 34 (23.9%) with abnormal umbilical cord pH, low Apgar score or admission to NICU for ≥ 24 hours.

7.4.2 Adverse perinatal outcome

The maternal and pregnancy characteristics of those with adverse neonatal outcome are compared to those without such outcome in Table 7.1. In pregnancies with adverse perinatal outcome, compared to those without, there was a higher prevalence of women of Black racial origin, a lower incidence of cigarette smokers, parous women with previous vaginal birth, lower median MCA-PI MoM and CPR MoM. In pregnancies with adverse perinatal outcome, compared to those without, median serum PLGF MoM was lower (0.44, IQR 0.30 - 0.82 vs 0.60, IQR 0.36-1.07; p=0.003), but median sFLT-1 MoM was not significantly different (p=0.080) (Figure 7.1).

Table 7.1 Maternal and pregnancy characteristics in pregnancies with adverse perinatal outcome compared to those without. Significance value* p<0.05; ** p<0.01.

Maternal and pregnancy characteristics	No adverse outcome (n=653)	Adverse outcome (n=142)
Maternal age in years, median (IQR)	28.6 (24.6-32.6)	29.5 (25.6-33.6)
Maternal BMI, kg/m^2, median (IQR)	31.5 (27.5-35.8)	31.9 (27.8-36.7)
Cigarette smoker, n (%)	96 (14.7)	12 (8.5) *
Racial origin		
White, n (%)	604 (92.5)	127 (89.4)
Black, n (%)	11 (1.7)	9 (6.3) **
South Asian, n (%)	27 (4.1)	5 (3.5)
East Asian, n (%)	5 (0.8)	0
Mixed, n (%)	6 (0.9)	1 (0.7)
Conception		
Spontaneous, n (%)	632 (96.8)	133 (93.7)
Assisted conception, n (%)	21 (3.2)	9 (6.3)
Obstetric history		
Nulliparous, n (%)	279 (42.7)	95 (66.9)
Parous, previous CS, n (%)	31 (4.7)	13 (11.3) **
Parous, previous VD, n (%)	343 (52.5)	31 (21.8) **
Pregnancy complications		
Gestational diabetes, n (%)	50 (7.7)	13 (9.2)
Obstetric cholestasis, n (%)	35 (5.4)	7 (4.9)
Gestational hypertension, n (%)	16 (2.5)	5 (3.5)
Preeclampsia, n (%)	7 (1.1)	4 (2.8)
Fetal-placental biomarkers		
UA PI in MoM, median (IQR)	1.00 (0.89-1.14)	1.06 (0.90-1.17)
UA PI >90th percentile, n (%)	106 (16.2)	29 (20.4)
MCA PI in MoM, median (IQR)	0.97 (0.84-1.12)	0.95 (0.81-1.05) *
MCA PI <10th percentile, n (%)	137 (21.0)	40 (28.2)

CPR in MoM, median (IQR)	0.97 (0.80-1.14)	0.89 (0.72-1.12) **
CPR <10th percentile, n (%)	143 (21.9)	40 (28.2)
PLGF in MoM, median (IQR)	0.60 (0.36-1.07)	0.44 (0.30-0.82) *
PLGF < 10th percentile, n (%)	305 (46.7)	84 (59.2) **
sFLT-1in MoM, median (IQR)	1.19 (0.85-1.79)	1.31 (0.91-2.14)
sFLT-1 > 90th percentile, n (%)	166 (25.4)	47 (33.1)
GA at delivery (weeks), median (IQR)	40.1 (39.0-41.4)	40.2 (39.2-41.5)
Birth weight in g, median (IQR)	3470 (3097-3820)	3495 (3010-3882)
Birth weight <10th percentile, n (%)	124 (19.0)	35 (24.6)

BMI=Body mass index; CS=caesarean section; VD=vaginal delivery; UA=Umbilical artery; MCA=Middle cerebral artery; CPR=Cerebroplacental ratio; PLGF=Placental growth factor; sFLT-1=Soluble fms-like tyrosine kinsase-1

Univariable regression analysis demonstrated that in prediction of adverse perinatal outcome, there was a significant contribution from Black racial origin, parous women with a previous vaginal delivery, UA-PI MoM, MCA-PI MoM, CPR MoM and PLGF MoM (Table 7.2). Multivariable regression analysis demonstrated that in prediction of adverse perinatal outcome there was a significant contribution from maternal age, Black racial origin, parous women with a previous vaginal birth, women who developed PE, and CPR MoM (R2=0.146; p<0.001) but not PLGF MoM (p=0.214) or sFLT-1 MoM (p=0.714) (Table 7.2). The performance of screening by history alone in prediction of adverse perinatal outcome (DR 28.9% at FPR of 10%) was not improved by the addition of CPR (DR 33.8% at FPR of 10%) (AUROC: 0.702, 95% CI 0.654-0.750 vs. 0.712, 95% CI 0.664-0.760; p=0.233).

Table 7.2. Univariate and multivariate logistic regression analysis in prediction of adverse perinatal outcome

Maternal and pregnancycharacteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal age – 30 (years)	1.030 (0.999-1.063)	0.062	1.053 (1.018-1.088)	0.002
Maternal body mass index – 32 (kg/m^2)	1.017 (0.988-1.047)	0.246		
Cigarette smoker	0.536 (0.285-1.005)	0.052		
Racial origin				
White	1.000 (Reference)			
Black	3.891 (1.580-9.585)	0.003	4.589 (1.730-12.175)	0.002
South Asian	0.881 (0.333-2.331)	0.798		
Mixed	0.793 (0.095-6.641)	0.830		
Assisted conception	2.037 (0.912-4.546)	0.083		
Obstetric history				
Nulliparous	1.000 (Reference)			
Parous, previous CS	1.516 (0.794-2.894)	0.207		
Parous, previous VD	0.265 (0.172-0.410)	<0.001	0.216 (0.138-0.339)	<0.001
Pregnancy complications				
Gestational diabetes	1.215 (0.641-2.303)	0.550		
Obstetric cholestasis	0.916 (0.398-2.105)	0.835		

Gestational hypertension	1.453 (0.523-4.034)	0.473		
Preeclampsia	2.675 (0.772-9.263)	0.121	3.874 (1.037-14.478)	0.044
Fetal-placental biomarkers				
UA PI MoM	2.543 (1.016-6.364)	0.040		
MCA PI MoM	0.337 (0.130-0.876)	0.026		
Cerebroplacental ratio MoM	0.343 (0.162-0.729)	0.005	0.430 (0.194-0.951)	0.037
Placental growth factor MoM	0.748 (0.562-0.995)	0.046		
Soluble fms-like tyrosine kinase MoM	1.156 (0.973-1.374)	0.100		
Birth weight z-score	0.905 (0.801-1.022)	0.109		

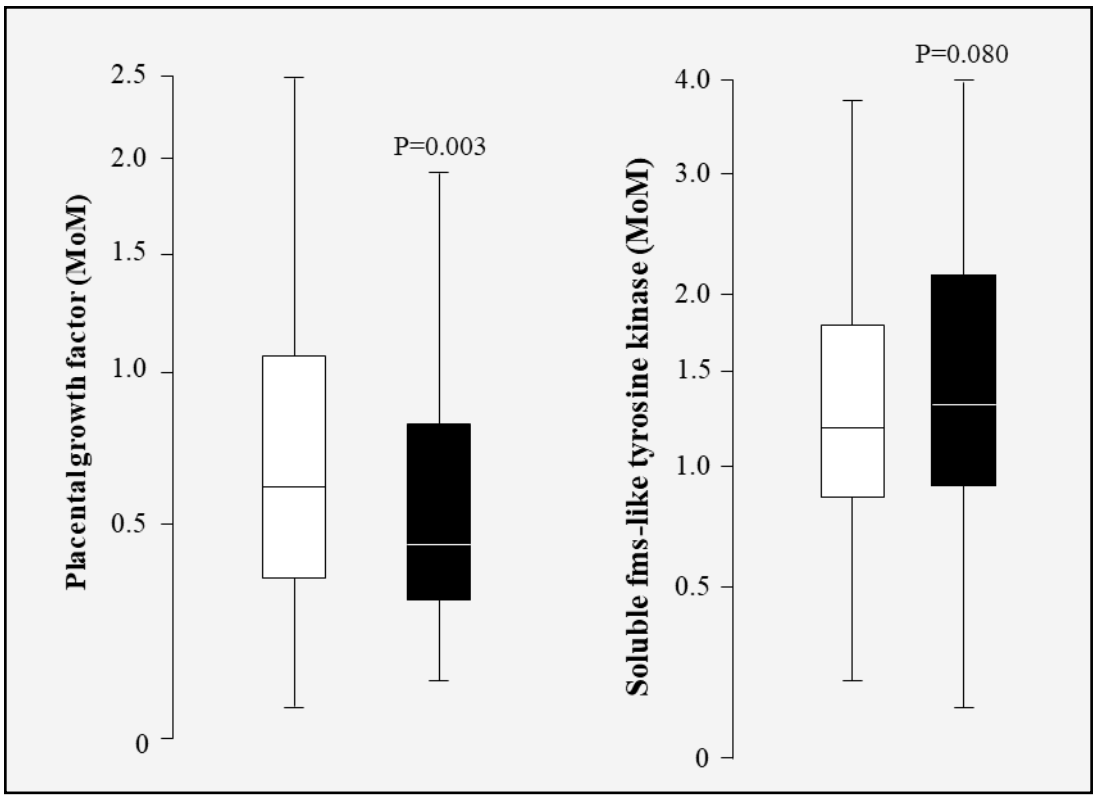


Figure 7.1 PLGF and sFLT-1 level in women who delivered vaginally (white box) compared to those who required a caesarean section for fetal distress (black box).

Chapter 8

Discussion

8 Chapter 8: DISCUSSION

8.1 Main findings of the study

The findings of my study demonstrate that the proportion of patients achieving vaginal birth following IOL was about 75%; 15% of patients required an instrumental delivery and 25% of women underwent a caesarean section for either failed induction or for failure to progress or for fetal distress. The study confirmed that maternal characteristics play an important role in predicting IOL success and the main factors include maternal age, weight, height, and parity; nulliparous women had a 10 times higher risk of CS for FTP following IOL when compared to multiparous women, the risk of CS in older women (age >40) and women with a higher BMI was twice compared to younger women with normal BMI. Women with a height < 144cm were 5 times more likely to have an unsuccessful IOL than women that were taller.

The detection rate for CS for FTP based on maternal factors and parity (DR 67% for FPR 20%) was only marginally improved by addition of cervical length at transvaginal ultrasound and head to perineum distance at transperineal ultrasound (DR 72% for FPR 20%). In my study, the cervical length prior to IOL was significantly shorter in women who achieved a vaginal birth (23mm) when compared to those who underwent a CS (26.8mm). Those women who failed their IOL had the longest mean cervical length measurement of 29.7mm.

The HPD was the shortest in women who delivered vaginally (71mm) when compared to those who required CS for FTP (78mm) or for failed IOL (81mm). In the study's cohort, mean Bishop score for women who achieved a vaginal birth was 5 and 6 in those who had an assisted vaginal birth with either forceps or ventouse. BS for women who required CS for any reason was 4. It remained 4 for women who failed their IOL and underwent CS for this reason. BS was 5 for women who required a CS for either failure to progress or for fetal distress. BS of < 4 for CS for either failed IOL or CS for failure to progress and BS > 4 for vaginal birth was statistically significant with p-value of 0.000067. The performance of BS compared to cervical length and head to perineum distance was not assessed as this was not one of my study objectives but remains an interesting research question.

The findings of this study of IOL demonstrate that about 80% of pregnancies requiring caesarean section for fetal distress in labour and those with adverse neonatal outcome deliver AGA neonates. Consequently, if a major contributor to these adverse events is impaired placentation the vast majority of such impairment is observed in association with AGA fetuses.

The study has also shown that there is a significant association between adverse perinatal outcome and CPR. This is not surprising because redistribution in the fetal circulation, with preferential blood flow to the brain at the expense of the viscera, has been demonstrated by cordocentesis to be associated with fetal hypoxemia and academia in both SGA and AGA fetuses. However, the performance of CPR in

screening for adverse perinatal outcome is poor even when the assessment is carried out within 24 hours of delivery.

A combination of maternal and pregnancy characteristics, including age, weight, racial origin, previous obstetric history, PE, gestational age at delivery and amniotic fluid volume, identified about 40% of the pregnancies requiring caesarean section for fetal distress, at FPR of 10%, and this performance of screening was not improved by addition of CPR. In screening by CPR <10th percentile the DR of caesarean section for fetal distress was 51% at FPR of 30% in SGA neonates and the respective values for non-SGA neonates were 24% and 20%. In the case of adverse neonatal outcome, the CPR was <10th percentile in 31% of SGA neonates at FPR of 34% and the respective values for non-SGA neonates were 35% and 20%.

Additionally, I found that an adverse perinatal outcome occurred in 18% of cases. In pregnancies with adverse perinatal outcome, compared to those without, there was a lower median MCA-PI MoM, CPR MoM and serum PLGF MoM, but not significantly different sFLT-1 MoM. Multivariable regression analysis demonstrated that the risk of adverse perinatal outcome increased with increasing maternal age and decreasing CPR, it was higher in women of Black racial origin than in White women and in those with PE and lower in parous women with previous vaginal birth than in nulliparous women. The performance of screening for adverse perinatal outcome by maternal risk factors, with DR of 29% at FPR of 10%, was not improved by the addition of any of the biomarkers of impaired placentation and fetal hypoxemia.

These findings suggest that first, low PLGF and CPR and high sFLT-1 provide poor prediction of impaired placentation and fetal oxygenation or second, the contribution of maternal and pregnancy characteristics as well as events in labour play a much greater role than impaired placentation in the development of fetal compromise in labour or adverse neonatal outcome. Alternatively, the selected outcomes of CS for non- reassuring fetal status in labour, low 5-minute Apgar score, low cord blood pH and admission to NICU for >24 hours, do not adequately reflect adverse perinatal outcome.

8.2 Strengths and limitations of the study

The strengths of my study are first, examination of a large number of pregnancies within 24 hours of IOL, second, inclusion of a consecutive series of pregnancies undergoing IOL at term without exclusions according to fetal size or pregnancy complication so that the results can be generalizable, third, measurement of MCA-PI and UA-PI by appropriately-trained doctors, and fourth, use of a wide range of well accepted indicators for adverse perinatal outcome. Additionally, measurement of sFLT-1 and PLGF were performed by automated machines and that provided reproducible results. The expression of the values of the biomarkers as MoMs after adjustment for maternal factors and reagents used that affect the measurements reduced the bias. I also used of a wide range of well accepted indicators of adverse perinatal outcome.

The main limitation of this as well as other previous studies is the use of caesarean section for fetal distress and adverse neonatal outcome as surrogate markers of prelabour fetal hypoxia. It is therefore uncertain, whether the low performance of CPR in the prediction of these adverse outcomes is a reflection that CPR provides poor assessment of fetal oxygenation or that the contribution of maternal and pregnancy characteristics as well as events in labour play a much greater role than prelabour fetal oxygenation in the development of fetal distress in labour or adverse neonatal outcome. There is therefore, a potential inadequacy of the surrogate markers of adverse perinatal outcome that may be affected to a greater extent by events in labour and delivery rather than prelabour fetal oxygenation.

Another limitation of the study is that pregnancies undergoing IOL at term are preselected, because in some cases of SGA fetuses with abnormal Doppler results, elective delivery by caesarean section would have been carried out, had IOL been undertaken is such cases it is likely that some would have ended up with caesarean section for fetal distress and asphyxia at birth reflected in low Apgar score, low cord blood pH and admission to NICU. Consequently, the performance of screening by CPR for adverse perinatal outcome in SGA fetuses would have been negatively biased.

8.3 Comparison with findings from previous studies

The results of our study are similar to the previous studies reporting on clinical utility of CPR measured at 32- and 36-weeks' gestation, which demonstrate that the

performance of screening of CPR in prediction of adverse perinatal outcomes is poor with DR ranging from about 5 to 15%, at FPR of about 5%.

Two previous studies examined the value of CPR in predicting adverse outcome in pregnancies undergoing IOL at ≥ 37 weeks' gestation. One study examined 164 women with SGA fetuses and reported that the DR and FPR of pre-induction CPR <5th percentile were 70% and 46%, respectively, for caesarean section for fetal distress and 66% and 40% for adverse neonatal outcome. Another study in 151 AGA fetuses reported that the pre-induction CPR was not significantly different between those with operative delivery for intrapartum fetal compromise or umbilical arterial blood pH <7.0 and those with normal outcome; moreover, there was no significant association between CPR and cord blood pH.

Researchers examining the value of low CPR in predicting adverse outcome in pregnancies undergoing IOL at ≥ 37 weeks' gestation reported contradictory results. A study of 19,207 women with singleton pregnancies undergoing routine assessment at 35-37 weeks' gestation reported that serum PLGF < 5th percentile and sFLT-1 > 95th percentile were associated with increased risk of caesarean delivery for suspected fetal compromise in labour and NNU admission for ≥48 hours. However the performance of screening for these adverse outcomes from maternal factors and estimated fetal weight was not improved by the addition of these biochemical markers. Similarly, a study of 438 pregnancies reported that although PLGF measured at 38-40 weeks' gestation was lower in those with adverse intrapartum and neonatal outcomes

8.4 Conclusion and summary

The findings are consistent with previously published results worldwide. Maternal characteristics and obstetric history including previous vaginal delivery are the strongest predictors of successful IOL resulting in vaginal delivery. Addition of transabdominal ultrasound for fetal biometry, amniotic fluid volume and Doppler studies as well as transvaginal ultrasound for cervical length, posterior cervical angle, transperineal ultrasound for angle of progression and head to perineum distance and maternal blood for serum concentration of PLGF and sFLT-1, only marginally improve the prediction of adverse outcomes.

The performance of CPR in screening for adverse perinatal outcome is poor even when the assessment is carried out within 24 hours of delivery.

Serum PLGF and sFLT-1, measured within 24 hours of IOL, do not provide a significant additional contribution to maternal risk factors in the prediction of caesarean section for suspected fetal compromise in labour or surrogate markers of adverse perinatal outcome.

The definition of adverse perinatal outcomes is broad and includes both, maternal and neonatal complications. I have chosen widely accepted and clearly defined range of adverse perinatal outcomes, however, potentially variable interactions amongst those, may impact the overall result.

Assessment within 24h of labour induction determines woman's and fetus' condition at the time and it does not necessarily provide sufficient information on potential response to induction agents, length of labour and its progress. This may be influenced by the fetal occiput position, maternal mobility, modalities used for pain relief or even support in labour. The potential stress and unpredictable events in labour play an important role in development of fetal and maternal compromise leading to intervention.

Definition of fetal distress in labour has not been unified. Healthcare professionals providing maternity services and attending labours, often use the term - suspected fetal distress. Cardiotocography is the modality of choice used to assess fetal oxygenation in labour. However, its positive predictive value for hypoxia is only 30% and the inter observer variation is 30%. Acidosis post-delivery is diagnosed in only 50% of infants delivered due to pathological CTG trace. Additionally, there is a likely overlap between failure to progress resulting in prolonged first or second stage of labour and suspected fetal distress. The management of patients in labour vary between clinicians as well as patients expectations of labour and birth. Not only, the fear of possible patient's complaint but also potential adverse neonatal outcome and subsequent litigation may impact decision making.

Biochemical markers used to assess placentation may not be an adequate modality to determine fetal oxygenation and hypoxia in labour. PLGF and sFLT-1 used currently

in diagnosis of preeclampsia, may also be considered a marker of angiogenic placental syndrome. Both of these conditions impose a risk of maternal and/or fetal compromise in labour, but do not define it. Poor placentation is only one of the risk factors for fetal hypoxia in labour and it triggers continuous fetal monitoring. However, not all of the affected fetuses will show signs of oxygen starvation and will require an emergency delivery.

Both, failure to progress in labour and fetal distress are multifactorial. The combination of risk factors as well as biophysical and biochemical markers taken into consideration in this study, do not predict the above outcomes with accuracy required to be able to impose the potential risks and complications of an intervention, on mothers and their babies before undertaking a trial of vaginal delivery. Women have different perspectives and desires for the birth of their babies. Some, are keen to undergo a longer process and delay their labour in order to give themselves the highest possible chance of achieving a successful vaginal delivery, making this a priority. Others, however, may choose to be subjected to an intervention earlier, due to various reasons including tiredness, emotional and physical stress, as well as fear for their unborn child.

8.5 Implications for future research and practice

The results of my study demonstrate that the prediction of successful vaginal birth as well as adverse perinatal outcomes using a combination of maternal characteristics, biophysical and biochemical markers is modest. These models developed in this study

provide information for women undergoing IOL and gives them an objective overview of their chance of successful IOL. But the performance of such screening is poor and further studies need to be carried out in the future including more biomarkers to assess whether further improvement can be achieved in such prediction models.

Transperineal measurements of head to perineum distance and angle of progression prior to IOL and during labour, have been studied and the results are promising. It has a potential of improving women's experience in labour and reduce the number of digital vaginal examinations without compromising care. The implementation of additional ultrasound scans at the time of vaginal examination in labour could be time consuming and it requires substantial staff training. Further studies need to be undertaken to review how these examinations can supplement clinical assessments and provide more objective and accurate assessment of progress in labour.

The performance of CPR in screening for adverse perinatal outcome is poor even when the assessment is carried out within 24 hours of delivery. However, there are two potential benefits of measuring fetal CPR; first, to identify pregnancies that are at such high-risk of developing fetal distress in labour or an adverse neonatal outcome as a result of being subjected to labour, that are better managed by elective caesarean section and second, to stratify the intensity of monitoring during labour with high intensity for those with low CPR and low intensity for those with normal CPR.

Serum PLGF and sFLT-1, measured within 24 hours of IOL, do not adequately reflect neither placental angiogenic syndrome nor prelabour fetal hypoxia, which would lead to fetal distress in labour or neonatal adverse outcomes diagnosed post-delivery. Consequently, measurement of these metabolites is unlikely to be clinically useful in pregnancies undergoing IOL.

Chapter 9

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9 Chapter 9: References

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Appendix I: Prediction of Pregnancy Outcome Following Induction of Labour – Study protocol.

Prediction of Pregnancy Outcomes Following Induction of Labour

Protocol Short Title: POPIN Study

ISRCTN: 10984408

REC Number: 16/00/0367

Investigators

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1. Synopsis

Title of study	Prediction of Pregnancy Outcomes following Induction of Labour
Short Title	POPIN study
Sponsor name	Medway NHS Foundation Trust
Chief Investigator	Ranjit Akolekar
REC number	16/00/0367

Public Registry	ISRCTN: 10984408
Medical condition	Labour and delivery
Primary objectives	To develop a model to predict vaginal delivery after induction of labour based on maternal factors, biophysical and biochemical markers
Secondary objectives	To develop models to predict the following complications following induction of labour: Caesarean section for fetal distress Caesarean section for failure to progress Maternal complications such as post-partum haemorrhage and chorioamnionitis Neonatal complications such as admission to NNU, abnormal 5-minute Apgar score and abnormal umbilical cord pH To evaluate the effectiveness of ultrasound-based assessment of progress of labour in the prediction of successful vaginal delivery compared to assessment based on digital vaginal examination
Study Design	Prospective Observational Study
Sample Size	1000 women
Eligibility criteria	Singleton pregnancy Cephalic presentation Induction of labour Informed and written consent
Version / date	Version 1.5, 5th February 2016

CONTENTS

2. Background & Rationale

Background

Overview

Induction of labour (IOL) is one of the most common obstetric procedures and is carried out in 20-30% of pregnancies (NICE 2008, ACOG 2009, Mealing *et al.,* 2009). There is evidence that more than a third of women having IOL will need either an instrumental delivery or a caesarean section (CS) (NICE 2008).

A model that could accurately predict which women will have a successful IOL would be of significant benefit in counselling women prior to induction.

Current methods for predicting successful induction of labour

The Bishop score is the most commonly used clinical assessment prior to IOL. Unfortunately, it is subjective and with significant inter- and intra-observer variability and its utility at predicting induction-to-delivery interval and mode of delivery is limited (Faltin-Traub *et al.,* 2004; Peregrine *et al.,* 2006; Texeria *et al.,* 2012). A recent systematic review of 40 studies reporting results from more than 13,000 women concluded that for prediction of caesarean section, the use of Bishop score was associated with a poor sensitivity and specificity and therefore it should not be used to decide whether to induce labour or not (Kolkman *et al.,* 2013).

Newer methods for predicting successful induction of labour

There is evidence from studies that successful vaginal delivery can be predicted from maternal characteristics and components of obstetric history (Braveman *et al.,* 1995; Sebire *et al.,* 2001; Rane *et al.,* 2003; Rao *et al.,* 2008). This prediction can be further improved by the addition of pre-induction measurement of cervical length by transvaginal ultrasound scan (TVUS) (Ware and Raynor 2000; Pandis *et al.,* 2001; Rane *et al.,* 2003; Bueno *et al.,* 2005, Crane 2006, Peregrine *et al.,* 2006). Biochemical markers such as fetal fibronectin (fFN) have been examined in some studies as a potential marker for successful IOL but the reports from these studies are contradictory with some suggesting that it improves the prediction whereas some reporting that it was similar to Bishop score in its performance (Blanch *et al.,* 1996; Roman *et al.,* 2004; Crane 2006 Sciscione *et al.,* 2015). However, the majority of these studies have used qualitative rather than quantitative fFN. There are no studies that have examined the combination of fFN with maternal characteristics or with cervical length. Another biochemical marker which has been reported to predict spontaneous vaginal delivery is placental alpha macroglobulin-1 (PAMG-1) and some studies suggest that it can predict the onset of spontaneous delivery in women with threatened preterm labour (Lee *et al.,* 2012; Nikolova *et al.,* 2014; Ehsanipoor *et al.,* 2015). There is evidence that women in labour at term who have detectable PAMG-1 in cervicovaginal fluid have shorter admission-to-delivery interval (Lee *et al.,* 2009). However, there are no reported studies examining successful vaginal birth in women prior to IOL.

Current method for assessing progress in labour

The current method of assessing progress in labour is based on digital vaginal examination (VE) for cervical dilatation, fetal head position and fetal head descent (station). These observations are all recorded at each assessment and serially plotted on a graph over time (partogram) to examine the progress of labour (Friedman 1954). However, there is evidence from studies that VE are subjective, imprecise, uncomfortable for women and associated with infection, which have led to a recommendation for research into methods that can limit their use (Westoverv *et al.*, 1995, Seaward *et al.*,1998, Ying Lai *et al.*, 2002, Dupuis *et al.*, 2005, Buchmann *et al.*, 2007, NICE 2007).

An objective, reliable, non-invasive method of accurately predicting successful vaginal delivery and assessing progress in labour may potentially improve prediction of outcome and is likely to be more acceptable to women.

New methods for assessing progress in labour

A number of new techniques have recently been described using transperineal ultrasound assessments (TPUS) to monitor labour progress (Eggebo *et al.,* 2006; Barbera *et al.,* 2009; Hassan *et al.,* 2014). TPUS measurements are acquired by placing an ultrasound transducer on the patient's perineum to obtain images and take measurements. It is non-invasive and well tolerated by patients (Hassan *et al.*, 2014, Alvarez-Colomo *et al.,* 2015). The angle of progression (AOP) is a quantitative measurement of the angle from the leading part of the fetal skull and the symphysis

pubis (Barbera *et al.,* 2009). It correlates with clinical estimation of fetal station and is useful in predicting successful instrumental delivery (Kalache *et al.,* 2009; Duckelman *et al.,* 2010; Molina *et al.,* 2010; Tutschek *et al.,* 2011). The head-to-perineum distance (HPD) is a linear measurement of the distance from the leading part of the fetal skull to the perineum (Eggebo *et al.,* 2006). It correlates with fetal station and time to delivery, and is useful in predicting successful vaginal delivery in prolonged labour (Eggebo *et al.,* 2008; Torkildsen *et al.,* 2011; Chan *et al.,* 2015). A simple method based on two-dimensional ultrasound to measure sonographic cervical dilatation (SCD) has recently been reported. The authors report that satisfactory views of SCD can be obtained from 1 cm to full dilatation of the cervix and that there is a good concordance with conventional digital VE (Hassan *et al.,* 2013 and 2014). The studies suggest that assessment of progress of labour is feasible in most cases but the results were based on studies with a small sample size (n=52) (Hassan *et al.,* 2014).

All of the above techniques have been studied in small populations of women, and no study has evaluated all of these measurements in a large population throughout labour.

We propose to develop a model that will accurately predict induction to delivery interval and risk of caesarean section using a combination of maternal and fetal factors measured at a pre-induction clinic. Additionally we will systematically measure the AOP, HPD and SCD in a large population of women throughout labour following IOL. After defining the reference range for each measurement, we aim to develop a

sonographic partogram and compare its performance in the prediction of successful vaginal delivery with conventional partogram that is based on clinical VEs.

Proposed study

Overview

Women undergoing IOL and meeting the eligibility criteria will be invited to participate in a research study on predicting pregnancy outcomes following IOL. Those agreeing to participate will have additional ultrasound measurements taken at a pre-induction clinic, a maternal blood sample and vaginal swabs prior to IOL. They will also be offered serial ultrasound assessments during labour until delivery. After birth, a sample of umbilical cord blood and placental tissue will be stored for future research.

Current clinical practice

At Medway Maritime Hospital, all women with singleton pregnancies booked for IOL attend a pre-induction clinic as part of routine clinical practice. The clinic is held from Monday to Friday and women attend for an appointment a day prior to IOL.

In the pre-induction clinic, women have a transabdominal (TA) ultrasound assessment to confirm fetal presentation, estimate fetal weight, measure amniotic fluid index and assess fetal well-being using fetal Doppler indices. A blood sample is obtained via venepuncture to check up-to-date full blood count and save a blood sample for blood

grouping prior to commencing IOL. They are offered a TVUS to measure cervical length prior to digital VE to assess the Bishop Score. A computerised cardiotocography (CTG) is performed to ensure fetal well-being. Women are provided an information leaflet about IOL and given an appointment to attend for administration of induction agent. The next day, women attend the induction suite for clinical assessment when they have a VE and administration of the induction agent. A computerised CTG is carried out and if satisfactory, women are offered inpatient admission or outpatient management based on their indication for IOL. Women are allowed to mobilise and expectant management is continued for the next 24 hours or until they are in active phase of labour, whichever is earlier. At this point, a VE is repeated and cervical dilatation is assessed. If the cervix is favourable for artificial rupture of membranes (ARM) or if the women are already in active labour, then they are transferred to the delivery suite for further management.

The onset of active phase of labour is defined by commencement of 3-4 regular uterine contractions every 10 minutes each lasting for 45-60 seconds and / or a cervical dilatation of 3 cm. From this point on, a graphical record of progress in labour is maintained on the partogram and progress of labour is assessed by regular abdominal and VE done every 4 hours unless there are complications such as fetal distress.

Research Study

Assessments prior to labour

We will invite women attending the pre-induction clinic to participate in the research study involving prediction of pregnancy outcomes following IOL. After obtaining informed written consent, maternal history and demographics will be recorded on an electronic clinical records form (CRF). A TPUS will be performed along with the routine ultrasound assessment to check position of occiput, AOP, HPD and SCD.A speculum examination will be performed to obtain vaginal swabs for measurement of quantitative fFN and PAMG-1. An additional bottle of blood will also be collected and stored for future research to examine potential biomarkers of adverse outcomes. When women attend the induction suite, they will be offered a TPUS prior to administration of the induction agent to measure AOP, HPD, SCD and check position of occiput.

Assessment in labour

When women are diagnosed to be in active phase of labour, they will be offered TA and TPUS immediately prior to routine clinical examinations and VE every 4 hours until delivery. The measurements in labour will be made using a Voluson P8 BT124 ultrasound machine and a 4C-RS probe. The measurements of fetal head position, AOP, HPD and SCD will be made using manual and automated measurements as previously described (Akmal et al., 2002; Eggebo et al., 2006; Barbera et al., 2009; Hassan et al., 2013). Fetal well-being will be assessed using Doppler assessment fetal blood vessels. All of the above measurements will be stored in a secure electronic file for later analysis.

3. Study Objectives and Design

3.1. Study Objectives

Primary

To develop a model to predict successful IOL based on maternal factors, biophysical and biochemical markers

Secondary

To develop models to predict the following complications following IOL:

- Caesarean section for fetal distress
- Caesarean section for failure to progress
- Maternal complications such as post-partum haemorrhage and chorioamnionitis
- Neonatal complications such as admission to NNU, abnormal 5-minute Apgar score and abnormal umbilical cord pH

To evaluate the effectiveness of ultrasound-based assessment of progress of labour in the prediction of successful vaginal delivery compared to assessment based on digital vaginal examination

3.2 Study Design

Prospective observational study in a single maternity unit in the UK.

4. Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

5. Women attending the pre-induction clinic for IOL
6. Singleton pregnancies
7. Cephalic presentation
8. Informed and written consent

4.2 Exclusion Criteria

6. Multiple pregnancies
7. Women with fetal demise
8. Women less than 18 years
9. Women who are unconscious or severely ill, those with learning difficulties, and serious mental illness
10. Malpresentation

4.3 Selection of Participants

This will be a study involving a single maternity unit in the UK. Women who fulfil the eligibility criteria that are due to undergo IOL will be approached. They will receive an information leaflet and counselling concerning the study and those agreeing to take participate will be invited and requested to sign a consent form.

4.4 Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. If subject wishes to withdraw from the study (request that her data are not used for research), this will not affect her care during their pregnancy. All efforts will be made to report the reason for withdrawal as thoroughly as possible.

4.5 Expected Duration of Study

The anticipated duration of the study from enrolment of the first subject to completion of the final report to the REC is 18 months.

5. Study Procedures

5.1 Informed Consent

All potential participants will be provided a patient information leaflet and a consent form describing this study and providing sufficient information for them to make an informed decision about their participation in this study. The patient information leaflet and consent form will be submitted with the study protocol for review and approval by the REC for the study. The formal informed consent, using the REC-approved consent form, must be obtained before any potential participant is submitted to any study procedure. This consent form will be signed by the participant and the investigator-designated research fellow obtaining the consent.

5.2 Clinical Procedures

Women agreeing to participate in the study will have their routine care managed by clinical staff in the pre-induction clinic before the process of IOL and once women are in active labour, the management will be provided by the on-call team of obstetricians and midwives according to standard hospital guidelines and protocols. The research team will not provide any input towards routine clinical management of women.

5.3 Laboratory Testing Procedures

A Dacron swab will be used to collect cervicovaginal secretions from the posterior fornix of the vagina (10 seconds) during a sterile speculum examination. One aliquot (200 μl) of the sample will be analysed by the quantitative Rapid fFN 10Q analyser (Hologic™) according to manufacturer's instructions. The sample will be discarded following testing. Similarly, a sterile flocked vaginal swab provided with PartoSure test kit (PartoSure™ Test) is inserted into the vagina (no more than 5-7 cm) and removed after 30 seconds. The sample is then tested according to manufacturer's instructions. The sample will be discarded following testing.

Maternal blood sample will be collected via standard venepuncture into BD Vacutainer blood collection tubes. The serum and plasma will be stored at -80°C for later analysis into biomarkers of adverse pregnancy outcome. Similarly, umbilical cord venous blood will be collected after delivery into BD vacutainer tubes and serum and plasma

stored at -80°C for analysis. A sample of placental tissue will be obtained and stored in RNA later solution at -80°C for analysis.

5.4 Follow-up Procedures

Women will be requested to complete a questionnaire about the study. The questionnaire is aimed to understand women's views regarding assessments prior to IOL and during labour. The questions provide a comprehensive assessment of the acceptability to women of transperineal ultrasound scans and to understand and quantify their views about acceptance and potential psychological morbidity associated with these assessments. In particular, there is a detailed assessment of pain and anxiety associated with transperineal scans and routine vaginal examinations; both before and after the examination is undertaken.

Validated questionnaires were used for assessing pain and anxiety; the six-item short form of the state scale of the Spielberger State-trait Anxiety Inventory (STAI) was used to assess women's retrospective views regarding their levels of anxiety before and after these assessments (Marteau and Bekker, 1992; Julian 2011). Unidimensional and multidimensional scales were used to assess pain or discomfort associated with these examination before and after they were carried out (Younger et al., 2009). The unidimensional assessment was undertaken using a numerical rating scale (NRS) which consisted of a score of 0 to 10, with 0 being no pain and 10 being the worst pain. Multidimensional assessment of pain was assessed using The Present Pain Intensity (PPI) of the short form of the McGill Pain Questionnaire (SF-MPQ) (Melzack 1987).

6. Assessment of Safety

6.1 Anticipated Risks

No aspects of the research study are likely to be associated with any significant risks or harm. The patients may experience mild discomfort during the routine assessments such as phlebotomy or ultrasound examination, which are a part of routine clinical practice.

6.2 Medical Monitoring for Participant Safety

The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events.

7. Statistics

7.1 Sample Size

Medway Maritime Hospital currently performs approximately 1,500 inductions each year. We would hope for a recruitment rate of approximately 70%, which would enable us to enrol around 1000 patients within a year. No formal sample size calculation is appropriate here, and the rationale for this anticipated number of participants is such: this is an exploratory study where the main objectives are to develop predictive models for various outcomes of induction. In order to maximise the reliability of any models proposed, these should be based on a large number of observations. Most of

the data we aim to gather will be routinely collected as part of the IOL procedure. Where we ask patients to undergo additional non-routine procedures, these will be clearly identified and patients will have the opportunity to consent (or not) to some or all of the additional procedures without their normal standard of care being affected in any way.

7.2 Data Analysis

Data summaries for continuous variables will be expressed as median and interquartile ranges and for categorical variables will be expressed as n (%). Parametric (e.g. t tests) and non-parametric statistics (e.g. Mann-Whitney U-test) will be used to compare differences in the continuous and non-continuous variables respectively, between groups. Chi-square test or Fisher's exact test will be used to examine associations between categorical variables. Univariate and multivariate regression analysis will be used to examine relationships between outcome and predictor variables, where appropriate, and to determine the significance of predictor variables in prediction of adverse outcomes. Area under receiver operating characteristic curves (AUROC) will be used to determine the detection rates and false positive rates for the prediction models.

8. Direct Access to Source Data and Documents

The Investigator(s) will permit study-related monitoring, audits, NREC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, blood test reports, ultrasound reports).

9. Ethics & Regulatory Approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework. This protocol and related documents will be submitted for review to NREC. Annual progress and a final report at conclusion of the study will be submitted to the NREC within the timelines defined in the Regulations.

10. Quality Assurance

Monitoring of this study to ensure compliance with GCP and scientific integrity will be managed and oversight retained by the R&D Quality Team.

11. Data Handling

The Principal Investigators will act as custodian for the study data. The following guidelines will be strictly adhered to: Patient data will be anonymised and stored on a password-protected computer. All study data will be stored in line with the Data

Protection Act. The Sponsor-Investigator will retain the specified records and reports for up to 5 years.

12. Data Management

13.1 Source Documents

Source Data are the record of patients' demographic data, ultrasound scan and clinical findings and observations and other information contained in Source Documents. Source Documents are the original data in the Voluson P8 as well as the patient's medical record. When applicable, information recorded on the case report form (CRF) shall match the Source Data recorded on the Source Documents.

13.2 Case Report Form

The study electronic CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done we will write "N/D". If the item is not applicable to the individual case, we will write "N/A". All entries will be entered electronically.

A paper CRF will be used alongside the primary electronic CRF. If any entry error has been made to the paper CRF, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and

dated. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialled and dated.

A paper CRF will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

13. Insurance / Indemnity

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the study who have honorary contracts with the relevant NHS Trust.

14. Financial Aspects

The study will be supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116).

Appendix II: Ethical approval for study from NHS Health Research Authority (HRA)

NHS
Health Research Authority
London – Dulwich Research Ethics Committee
Health Research Authority
Skipton House
80 London Road
London SE1 6LH

Tel: 020 7104 8113
Email: nrescommittee.london-dulwich@nhs.net

31 March 2016

Mr Ranjit Akolekar
Consultant in Fetal Medicine and Obstetrics
Medway NHS Foundation Trust
Fetal Medicine Unit
Medway Maritime Hospital
Windmill Road
Kent ME7 5NY

Dear Mr Akolekar,

Study title:	**Prediction of Pregnancy Outcomes Following Induction of Labour**
REC reference:	**16/LO/0367**
Protocol number:	**799**
IRAS project ID:	**198121**

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mr Michael Higgs, nrescommittee.london-dulwich@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper		08 February 2016
Covering letter on headed paper		20 March 2016
Covering letter on headed paper		29 March 2016
Covering letter on headed paper		30 March 2016
Letter from funder		08 February 2016
Letter from sponsor		08 February 2016
Letter from statistician		04 February 2016
Non-validated questionnaire [Patient Questionnaire]	1.0	15 March 2016
Participant consent form	1.2	15 March 2016
Participant information sheet	1.7	30 March 2016
REC Application Form [REC_Form_08022016]		08 February 2016
Referee's report or other scientific critique report [Independent peer review]		08 February 2016
Research protocol or project proposal [Study protocol]	1.6	15 March 2016
Summary CV for Chief Investigator (CI) [Ranjit Akolekar CV]		08 February 2016
Summary CV for student [Alex Frick CV]		08 February 2016
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary and flow chart]	1.0	08 February 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments

- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/LO/0367	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Michael Philpot
Chair

Email:nrescommittee.london-dulwich@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Robert Hughes, Medway NHS Foundation Trust*
Dr Alexander Frick, Harris Birthright Research Centre for Fetal Medicine

Appendix III: Patient information leaflet

Medway NHS
NHS Foundation Trust

Patient information sheet
Version 1.7; 30th March 2016

Study title: Prediction of Pregnancy Outcomes following Induction of Labour

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take your time to read the following information carefully and discuss it with friends or relatives if you wish. If you have any questions or require any further information please contact the research team.

What is the purpose of the study?
About a third of women need induction of labour. Although the aim of induction is to achieve a vaginal delivery, some women may not be successful and end up having a caesarean section. Currently, there are no effective methods to predict which women will not respond favourably to induction of labour or how long this process is likely to take. The purpose of this study is to develop methods to predict whether induction will result in vaginal delivery or caesarean section.

Why have I been offered participation in this study?
You have been invited to participate because you are pregnant and you have been scheduled for an induction of labour. At Medway Maritime Hospital, we systematically review women in a specialist Pre-Induction Clinic to examine your baby's growth and well-being and assess your suitability for induction.

Do I have to take part?
It is your choice whether or not to take part in the study. If you decide to participate, we will give you this information leaflet to keep and request you to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the care you receive, either in the Pre-Induction Clinic or in labour.

What happens in the Pre-induction Clinic if I take part in the study?
If you decide to take part then along with your routine clinical assessments in the Pre-induction clinic, which involves an ultrasound examination of the baby, digital vaginal examination and a blood test, we will offer you an ultrasound scan to measure the length and dilation of the neck of the womb (cervix) and to find out how low is the baby's head in the pelvis. We will take a vaginal swab to carry out tests which we hope will improve the prediction of the success of induction. You will have a blood test as part of routine assessment and we will take a sample of blood to check for markers which will help us to predict the outcome of the induction.

What does this study require me to do during my labour?
You will be cared for in the same way as everyone else during your induction and labour. This includes regular vaginal examinations which are used to help assess how your labour is progressing. If you agree to participate in the study, with your consent we would like to perform a transabdominal and transperineal scan before each vaginal examination to obtain information about the baby's well-being, the position of the baby's head and the dilatation of the cervix. The transperineal ultrasound examination is a non-invasive examination which involves placing the ultrasound probe on the perineum to obtain required measurements. The ultrasound examination will take up to approximately 5-7 minutes to complete. You will be offered these examinations

Medway NHS
NHS Foundation Trust

prior to the routine clinical assessment in labour, which are usually every 4 hours until you deliver. The doctors and midwives in the delivery suite managing your labour will not be aware of the study findings and the researchers will not be involved in making decisions regarding your labour and delivery. After the baby has delivered, the placenta and umbilical cord are usually discarded. If you agree to participate in the study, we will collect a small sample of placenta and umbilical cord blood to be used for future research. We are interested in your experience of the transperineal scan so at the end of the study participation, we will ask you to complete a short questionnaire.

What are the benefits of taking part?
The study will not affect the management decisions of your current pregnancy but the information we gain through this research will hopefully help improve the care of all pregnant women, especially those undergoing an induction of labour, by allowing us to identify who is likely to have a successful induction and to predict complications before they happen. It may help you in a later pregnancy.

Are there any risks?
No. The study does not pose any risks to you or your baby. You are likely to be reviewed by additional healthcare professionals during your labour but we will try to ensure that the same members of the research team are available. We will treat you with respect and ensure that your privacy and dignity are maintained. We will check that you are happy to continue to participate in the study throughout your labour.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions via switchboard 01634 830 000]. If you remain unhappy and wish to complain formally, you can contact the local Patient Advice and Liaison Service (PALS) at Medway Maritime Hospital on 01634 825004.

Will my records be kept confidential?
All information collected about you during this study will be kept strictly confidential. All information will be communicated or exchanged after removing your name and personal details.

What will happen to the results of the study?
Once the study is complete, the results will be published in a scientific medical journal. You will not be identified in any report or publication. You are welcome to request the results or copies of the publications of the study which we will happily make available.

Who is organising and funding the research?
The study is supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116).

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people called the National Research Ethics Committee to protect your interests. This study has been reviewed and given a favourable opinion by the London-Dulwich Research Ethics Committee.

Appendix IV: Patient consent form

Medway NHS
NHS Foundation Trust

Patient consent form
Version 1.2 15th March 2016

Study title: Prediction of Pregnancy Outcomes following Induction of Labour

PATIENT CONSENT FORM		Please Initial box
1.	I confirm that I have read and understood the information sheet dated 15th March 2016 (Version 1.5) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	
3.	I agree to a pre-induction assessment which includes a transperineal ultrasound scan and collection of a vaginal swab.	
4.	I agree to have a blood sample stored for future research on prediction of pregnancy complications.	
5.	I agree to have regular transabdominal and transperineal ultrasound scans during my labour, either immediately before or after routine clinical examinations.	
6.	I agree to have a sample of placental tissue and umbilical cord blood collected for future research after the baby is delivered.	
7.	I agree to complete a questionnaire about the research at the end of my participation in the study.	
7.	I understand that relevant sections of my medical notes and data collected during the study may be reviewed by authorised members of the research team or NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	

Consent for research study:

Name of patient……..…… Signature ……..……..……

Date……..……..

Researcher…… Signature……..……

Date……..……..

Interpreter……..... Signature……..……

Date……..……..

Patient consent form, Version 1.2, 15th March 2016

Appendix V Case record form

Medway NHS
NHS Foundation Trust

CASE RECORD FORM

Maternal demographic details			
Patient ID		Appointment date	
Name		Gestation	
DOB		Indication for IOL	

Pre-induction assessment			
EFW		Fibronectin	
Deepest pool		PAMG-1	
UA PI		HPD (cm)	
MCA PI		AOP (cm)	
Cervical length		SCD (cm)	

Assessment in labour – 1: State time of assessment			
HPD (cm)		VE - position	
AOP (cm)		VE - station	
SCD (cm)		VE - dilatation	

Assessment in labour – 2: State time of assessment			
HPD (cm)		VE - position	
AOP (cm)		VE - station	
SCD (cm)		VE - dilatation	

Assessment in labour – 3: State time of assessment			
HPD (cm)		VE - position	
AOP (cm)		VE - station	
SCD (cm)		VE - dilatation	

Pregnancy outcome			
Date of delivery		Cord pH	
Mode of delivery		APGAR-5	
Birth weight (gm)		NICU admission	

Signature: _____ Date: _____

Case record form, Version 1.0

Appendix VI: Full text of my article “Prediction of adverse perinatal outcomes by the cerebroplacental ratio in women undergoing induction of labour” published in Ultrasound in Obstetrics & Gynaecology.

Ultrasound Obstet Gynecol 2019; **53**: 473–480
Published online 4 March 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20173

Prediction of adverse perinatal outcome by cerebroplacental ratio in women undergoing induction of labor

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KEYWORDS: adverse neonatal outcome; cerebroplacental ratio; Cesarean section; Doppler ultrasound; fetal distress; induction of labor

ABSTRACT

Objective *To investigate the performance of screening for adverse perinatal outcome by the cerebroplacental ratio (CPR) measured within 24 h prior to induction of labor.*

Methods *This was a prospective observational study of 1902 singleton pregnancies undergoing induction of labor at ≥ 37 weeks' gestation. Doppler ultrasound was used to measure the pulsatility index (PI) in the umbilical artery (UA) and fetal middle cerebral artery (MCA) within 24 h before induction of labor. The measured UA-PI and MCA-PI and their ratio were converted to multiples of the median after adjustment for gestational age. Univariable and multivariable logistic regression analysis was used to determine whether CPR improved the prediction of adverse perinatal outcome provided by maternal characteristics, medical history and obstetric factors. The detection rate (DR) and false-positive rate (FPR) of screening by CPR were estimated for Cesarean section for presumed fetal distress and adverse neonatal outcome, which included umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7, admission to the neonatal intensive care unit for > 24 h or hypoxic ischemic encephalopathy.*

Results *A combination of maternal and pregnancy characteristics, including age, weight, racial origin, previous obstetric history, pre-eclampsia, gestational age at delivery and amniotic fluid volume, identified 39% of pregnancies requiring Cesarean section for fetal distress at a FPR of 10%; addition of CPR did not improve the performance of screening. In screening for adverse neonatal outcome by a combination of parity and CPR, the DR was 17% at a FPR of 10%.*

Conclusion *Low CPR, measured within 24 h prior to induction of labor, is associated with increased risk of Cesarean section for fetal distress and adverse neonatal outcome, but the performance of CPR for such surrogate measures of fetal hypoxic morbidity is poor. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Doppler assessment of impedance to flow in the umbilical artery (UA), fetal middle cerebral artery (MCA) and the ratio of the pulsatility index (PI) in these vessels, or cerebroplacental ratio (CPR), is used for assessment of fetal oxygenation. In the 1980s, studies of fetal blood obtained by cordocentesis in small-for-gestational-age (SGA) fetuses demonstrated that increased impedance to flow in the UA and decreased impedance to flow in the MCA are associated with fetal hypoxemia and acidemia[1–4]. Subsequent studies in SGA fetuses in the 1990s reported that low CPR was associated with adverse perinatal outcome, including higher rates of perinatal death, Cesarean section for fetal distress in labor, neonatal acidosis, 5-min Apgar score < 7 and neonatal intensive care unit (NICU) stay > 24 h[5–7]. Renewed interest in the CPR has been stimulated by the possibility that this index may be predictive of adverse perinatal outcome not only in SGA but also in appropriate-for-gestational-age (AGA) fetuses. Prior *et al.* measured the CPR in 400 pregnancies with an AGA fetus immediately before established labor and reported that CPR < 10th percentile, compared to CPR ≥ 10th percentile, was associated with a six-fold increased risk for delivery by Cesarean section for fetal distress and that, in the group with CPR > 90th percentile, none had Cesarean section for fetal distress[8]. Subsequent

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ORIGINAL PAPER

studies proposed that a low CPR can identify AGA fetuses that have not reached their growth potential as a consequence of suboptimal placental function[9], and that low CPR, measured within 2 weeks prior to birth, is associated with the need for operative delivery for presumed fetal compromise and with neonatal unit admission at term, regardless of fetal size[9–12]. However, these studies examined high-risk pregnancies and did not report on the performance of CPR in the prediction of adverse outcome.

A screening study in 30 870 women with a singleton pregnancy attending for a routine hospital visit at 30–34 weeks' gestation investigated the potential value of CPR in the prediction of adverse perinatal outcome and reported that, although there was an association between CPR and birth-weight *Z*-score, umbilical cord blood pH and admission to NICU, the performance of screening by CPR was poor, with a detection rate (DR) of 5–11% at a false-positive rate (FPR) of 5%[13]. A possible explanation for such poor performance of screening was that the adverse perinatal events at term were too remote from the gestational age at which CPR was assessed. However, another study of 6178 singleton pregnancies screened routinely at 35–37 weeks' gestation, also reported significant associations between CPR and indicators of adverse perinatal outcome but again the performance of screening by CPR was poor with DR of 6–15%, at FPR of 6%[14].

The objective of this study was to investigate whether the performance of screening by CPR for adverse perinatal outcome is improved by undertaking the assessment within 24 h prior to induction of labor.

METHODS

Study population

The data for this study were derived from a prospective observational study for prediction of adverse pregnancy outcome following induction of labor during the period 1 May 2016 to 31 July 2018, at Medway Maritime Hospital, Gillingham, UK. At our hospital, women booked for induction of labor attend the preinduction clinic within 24 h prior to administration of the induction agent. At this appointment, we record maternal characteristics and medical and obstetric histories, and perform an ultrasound scan to, first, determine presentation, second, estimate fetal weight from measurements of fetal head circumference, abdominal circumference and femur length[15], third, assess amniotic fluid volume by measurement of the deepest pool of fluid without any fetal parts, classifying oligohydramnios and polyhydramnios by a deepest pool of < 2 cm and > 8 cm, respectively, and, fourth, carry out transabdominal color Doppler for measurement of PI in the UA and MCA[16]. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[17,18].

We included singleton pregnancies that were booked for induction of labor at ≥ 37 weeks' gestation and delivered a phenotypically normal neonate. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

Patient characteristics

Recorded patient characteristics included maternal age, racial origin (white, black, South Asian, East Asian or mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or *in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension or pre-eclampsia, and obstetric history (nulliparous if no previous pregnancy ≥ 24 weeks or parous, with or without history of Cesarean section). Maternal weight and height were measured.

The indications for induction of labor were postdates ($n = 710$), maternal request ($n = 278$), diabetes mellitus or gestational diabetes ($n = 150$), obstetric cholestasis ($n = 86$), chronic hypertension, pre-eclampsia or gestational hypertension ($n = 84$), suspected SGA fetus ($n = 197$), reduced fetal movements ($n = 180$), suspected large-for-gestational-age fetus ($n = 72$), spontaneous prelabor amniorrhexis ($n = 98$), polyhydramnios ($n = 31$), maternal medical condition such as cardiac disease ($n = 12$) or antepartum hemorrhage ($n = 4$).

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal delivery or Cesarean section), indication for Cesarean section, birth weight, 5-min Apgar score, umbilical arterial or venous pH and details of admission to NICU. Adverse outcome was defined as, first, Cesarean section for presumed fetal distress in labor and, second, adverse neonatal outcome (umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7, admission to the NICU for > 24 h or hypoxic ischemic encephalopathy). Cesarean section for presumed fetal distress in labor was carried out if there was evidence of a pathological electronic fetal heart rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1. *In-utero* interventions were attempted based on standard local guidelines and depending on the urgency for delivery. Hypoxic ischemic encephalopathy was diagnosed when there was disturbed neurologic function with evidence of perinatal hypoxia reflected in either a 5-min Apgar score < 5 or UA cord pH < 7.0 or base deficit > 12 mmol/L, supported by neuroimaging evidence of acute brain injury.

Statistical analysis

Data are expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Mann–Whitney *U*-test and χ^2 test or Fisher's exact test were used for comparison of outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics and measurements of fetoplacental Dopplers provided a significant contribution in the prediction of Cesarean section for fetal distress and adverse neonatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height, were centered by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA-PI and MCA-PI and their ratio were converted to multiples of the median (MoM) after adjustment for gestational age[16]. The birth-weight *Z*-score was derived from the normal range for gestational age[15]. We estimated cut-offs for 5th, 10th, 90th and 95th percentiles for UA-PI, MCA-PI and CPR and determined the prevalence of abnormal Doppler values in each of the outcome groups. We examined the performance of CPR MoM in the subgroups of SGA fetuses (birth weight < 10th percentile) and non-SGA fetuses (birth weight ≥ 10th percentile). Predicted probabilities from logistic regression analysis were used to construct receiver–operating characteristics (ROC) curves to assess performance of screening for these adverse outcomes. The area under the ROC curve (AUC) for fetal Doppler alone was compared to that obtained using all factors[19].

The statistical package SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

During the study period, there were 1902 women who underwent induction of labor and met the inclusion criteria. There were 1408 (74.0%) vaginal deliveries and 494 (26.0%) that needed Cesarean section, including 47 (9.5%) for failed induction, 181 (36.6%) for failure to progress, 258 (52.2%) for fetal distress and eight (1.6%) for other indications.

Cesarean section for fetal distress

The maternal and pregnancy characteristics of those delivering by Cesarean section for fetal distress are compared to those with vaginal delivery in Table 1. In pregnancies that required Cesarean section for fetal distress, compared to those delivering vaginally, the median maternal age and weight were higher, there were higher incidences of women of black and South Asian racial origin, parous women with a previous Cesarean section, pre-eclampsia, oligohydramnios and polyhydramnios, and median gestational age at delivery and UA-PI MoM were higher, CPR MoM was lower,

Table 1 Maternal and pregnancy characteristics in pregnancies with vaginal delivery compared to those that had Cesarean section (CS) for fetal distress

Characteristic	*Vaginal delivery (n = 1408)*	*CS for fetal distress (n = 258)*
Maternal age (years)	28.7 (24.8–33.1)	29.8 (25.8–33.6)†
Maternal weight (kg)	83.8 (73.0–96.4)	88.2 (77.0–102.3)‡
Maternal height (m)	1.65 (1.61–1.70)	1.65 (1.60–1.68)
Cigarette smoker	200 (14.2)	27 (10.5)
Racial origin		
White	1283 (91.1)	217 (84.1)
Black	41 (2.9)	14 (5.4)†
South Asian	61 (4.3)	20 (7.8)†
East Asian	7 (0.5)	1 (0.4)
Mixed	16 (1.1)	6 (2.3)
Conception		
Spontaneous	1361 (96.7)	243 (94.2)
Assisted	47 (3.3)	15 (5.8)
Obstetric history		
Nulliparous	545 (38.7)	175 (67.8)
Parous, previous CS	61 (4.3)	27 (10.5)‡
Parous, no previous CS	802 (57.0)	56 (21.7)‡
Medical disorder		
Chronic hypertension	7 (0.5)	1 (0.4)
Diabetes mellitus	15 (1.1)	3 (1.2)
Pregnancy complication		
Gestational diabetes	87 (6.2)	21 (8.1)
Obstetric cholestasis	69 (4.9)	9 (3.5)
GH	33 (2.3)	5 (1.9)
Pre-eclampsia	17 (1.2)	10 (3.9)‡
Amniotic fluid volume		
Normal	1320 (93.8)	221 (85.7)
Oligohydramnios	47 (3.3)	22 (8.5)‡
Polyhydramnios	41 (2.9)	15 (5.8)†
Fetoplacental Doppler		
UA-PI MoM	1.03 (0.91–1.16)	1.06 (0.92–1.20)†
UA-PI > 90th percentile	269 (19.1)	64 (24.8)†
MCA-PI MoM	0.98 (0.85–1.14)	0.97 (0.82–1.09)
MCA-PI < 10th percentile	274 (19.5)	64 (24.8)†
CPR MoM	0.95 (0.80–1.13)	0.90 (0.74–1.10)‡
CPR < 10th percentile	310 (22.0)	76 (29.5)‡
GA at delivery (weeks)	40.1 (39.0–41.5)	40.5 (39.4–41.6)‡
Birth weight (g)	3460 (3087–3800)	3530 (3100–3873)
Birth weight < 10th percentile	264 (18.8)	55 (21.3)
Neonatal morbidity		
5-min Apgar score < 7	6 (0.4)	10 (3.9)‡
Low cord blood pH*	30 (2.1)	9 (3.5)
Admission to NICU > 24 h	20 (1.4)	18 (7.0)‡
Hypoxic ischemic encephalopathy	0 (0)	1 (0.4)

Data are given as median (interquartile range) or *n* (%). *Umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively. †$P < 0.05$. ‡$P < 0.01$. CPR, cerebroplacental ratio; GA, gestational age; GH, gestational hypertension; MCA, middle cerebral artery; MoM, multiples of the median; NICU, neonatal intensive care unit; PI, pulsatility index; UA, umbilical artery.

and there was a higher prevalence of UA-PI MoM > 90th percentile and CPR MoM <10th percentile.

Univariable regression analysis demonstrated that, in prediction of Cesarean section for fetal distress, there was a statistically significant contribution from maternal age and weight, black and South Asian racial origin, being parous with no previous Cesarean section, pre-eclampsia, gestational age at delivery, amniotic fluid volume, UA-PI MoM and CPR MoM (Table 2). Multivariable regression analysis demonstrated that, in prediction of Cesarean section for fetal distress, there was a statistically significant contribution from all of the above factors except UA-PI MoM ($P = 0.264$) ($R^2 = 0.209$; $P < 0.0001$) (Table 2).

In screening for Cesarean section for fetal distress by maternal factors and obstetric and medical history, the DR was 39.1% at FPR of 10%; addition of CPR did not improve the performance of screening (AUC, 0.767 (95% CI, 0.733–0.800) *vs* 0.763 (95% CI, 0.730–0.796); $P = 0.271$) (Figure 1). In prediction of SGA neonates, the performance of screening by maternal factors and obstetric and medical history (DR of 30.9% at FPR of 10%) was improved by the addition of CPR (DR of 34.5% at FPR of 10%; AUC, 0.658 (95% CI, 0.604–0.710) *vs* 0.672 (95% CI, 0.617–0.723); $P = 0.048$).

The CPR was < 10th percentile in 50.9% (28 of 55) of SGA neonates that were delivered by Cesarean section for fetal distress and in 29.9% (79 of 264) of SGA neonates that were born vaginally ($P = 0.003$). In the non-SGA neonates, the CPR was < 10th percentile in 23.6% (48 of 203) of those delivered by Cesarean section for fetal distress and in 20.2% (231 of 1144) of those that were born vaginally ($P = 0.263$).

Adverse neonatal outcome

The maternal and pregnancy characteristics of those with adverse neonatal outcome are compared to those without such outcome in Table 3. In pregnancies with

Table 2 Univariable and multivariable logistic regression analysis in prediction of Cesarean section (CS) for fetal distress using maternal and pregnancy characteristics

	Univariable analysis		*Multivariable analysis*	
Characteristic	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age – 30 (in years)	1.026 (1.004–1.050)	0.023	1.065 (1.038–1.093)	< 0.0001
Maternal weight – 88 (in kg)	1.014 (1.007–1.021)	< 0.0001	1.022 (1.013–1.031)	< 0.0001
Maternal height – 1.64 (in m)	0.986 (0.965–1.007)	0.202	0.956 (0.932–0.981)	0.001
Cigarette smoker	0.706 (0.461–1.081)	0.109		
Racial origin		0.014		
White	1.000 (reference)			
Black	2.019 (1.082–3.766)	0.027	2.444 (1.212–4.929)	0.013
South Asian	1.939 (1.147–3.277)	0.013	1.970 (1.092–3.552)	0.024
East Asian	0.845 (0.103–6.899)	0.875		
Mixed	2.217 (0.858–5.729)	0.100		
Conception				
Spontaneous	1.000 (reference)			
Assisted	1.787 (0.984–3.247)	0.057		
Obstetric history				
Nulliparous	1.000 (reference)			
Parous, previous CS	1.378 (0.850–2.237)	0.194		
Parous, no previous CS	0.217 (0.158–0.299)	< 0.0001	0.167 (0.118–0.236)	< 0.0001
Medical disorder				
Chronic hypertension	0.779 (0.095–6.356)	0.815		
Pre-existing diabetes mellitus	1.093 (0.314–3.801)	0.889		
Pregnancy complication				
Gestational diabetes	1.345 (0.819–2.210)	0.241		
Obstetric cholestasis	0.701 (0.346–1.423)	0.326		
Gestational hypertension	0.823 (0.318–2.219)	0.689		
Pre-eclampsia	3.299 (1.493–7.289)	0.003	3.102 (1.288–7.467)	0.006
Amniotic fluid volume		< 0.0001		< 0.0001
Normal	1.000 (reference)			
Oligohydramnios	2.796 (1.652–4.731)	< 0.0001	2.476 (1.381–4.441)	0.002
Polyhydramnios	2.185 (1.189–4.015)	0.012	3.443 (1.753–6.762)	< 0.0001
Fetoplacental Doppler				
Umbilical artery PI MoM	2.664 (1.386–5.122)	0.003		
Middle cerebral artery PI MoM	0.569 (0.288–1.125)	0.105		
Cerebroplacental ratio MoM	0.453 (0.262–0.781)	0.004	0.454 (0.249–0.828)	0.010
Birth-weight *Z*-score	0.987 (0.897–1.085)	0.782		
GA at delivery – 40 (in weeks)	1.179 (1.071–1.298)	0.001	1.166 (1.046–1.300)	0.006

GA, gestational age; MoM, multiples of the median; OR, odds ratio; PI, pulsatility index.

adverse neonatal outcome, compared to those without, there was a lower incidence of parous women with no previous Cesarean section, lower median MCA-PI MoM and CPR MoM, and higher prevalence of CPR MoM $< 10^{th}$ percentile.

Univariable regression analysis demonstrated that, in prediction of adverse neonatal outcome, there was a statistically significant contribution from parity, MCA-PI MoM and CPR MoM (Table 4). Multivariable regression analysis demonstrated that, in prediction of adverse neonatal outcome, there was a statistically significant contribution from parous women with no previous Cesarean section and CPR MoM but not MCA-PI MoM ($P = 0.522$) ($R^2 = 0.025$; $P = 0.001$) (Table 4). The performance of screening by history alone in prediction of adverse neonatal outcome (DR of 12.8% at FPR of 10%) was significantly improved by the addition of CPR (DR of 16.9% at FPR of 10%; AUC, 0.581 (95% CI, 0.514–0.647) *vs* 0.632 (95% CI, 0.573–0.692); $P = 0.028$) (Figure 1).

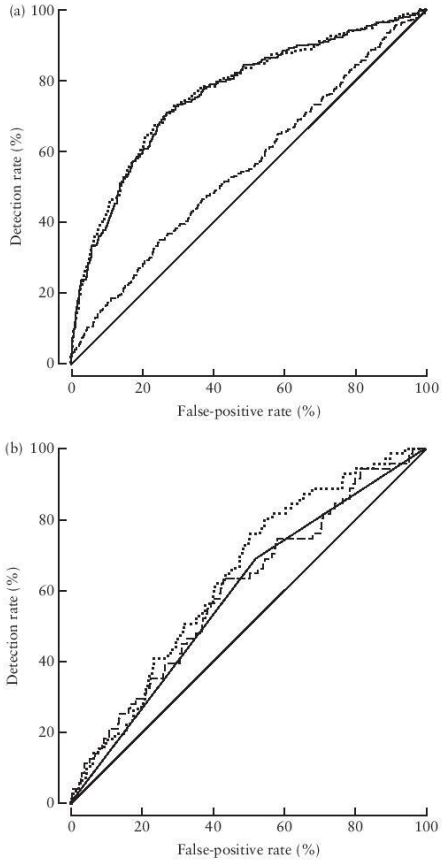

Figure 1 Receiver–operating characteristics curves for prediction of Cesarean section for fetal distress (a) and adverse neonatal outcome (b) by maternal factors (——), cerebroplacental ratio (– – –) and combination of the two (·····).

Table 3 Maternal and pregnancy characteristics in pregnancies with, compared to those without, adverse neonatal outcome

Characteristic	*No adverse neonatal outcome (n = 1819)*	*Adverse neonatal outcome (n = 71)*
Maternal age (years)	29.1 (25.0–33.3)	28.7 (25.2–32.8)
Maternal weight (kg)	85.0 (74.2–98.2)	86.0 (72.3–98.0)
Maternal height (m)	1.65 (1.61–1.69)	1.65 (1.61–1.69)
Cigarette smoker	243 (13.4)	9 (12.7)
Racial origin		
Caucasian	1640 (90.2)	63 (88.7)
Afro-Caribbean	60 (3.3)	3 (4.2)
South Asian	88 (4.8)	5 (7.0)
East Asian	9 (0.5)	0 (0)
Mixed	22 (1.2)	0 (0)
Conception		
Spontaneous	1745 (95.9)	67 (94.4)
Assisted	74 (4.1)	4 (5.6)
Obstetric history		
Nulliparous	834 (45.8)	44 (62.0)
Parous, previous CS	117 (6.4)	5 (7.0)
Parous, no previous CS	868 (47.7)	22 (31.0)‡
Medical disorder		
Chronic hypertension	8 (0.4)	0 (0)
Diabetes mellitus	21 (1.2)	1 (1.4)
Pregnancy complication		
Gestational diabetes	123 (6.8)	4 (5.6)
Obstetric cholestasis	84 (4.6)	3 (4.2)
GH	39 (2.1)	3 (4.2)
Pre-eclampsia	35 (1.9)	1 (1.4)
Amniotic fluid volume		
Normal	1673 (92.0)	63 (88.7)
Oligohydramnios	74 (4.1)	5 (7.0)
Polyhydramnios	72 (4.0)	3 (4.2)
Fetoplacental Doppler		
UA-PI MoM	1.03 (0.91–1.16)	1.07 (0.93–1.19)
UA-PI $> 90^{th}$ percentile	354 (19.5)	15 (21.1)
MCA-PI MoM	0.98 (0.84–1.12)	0.92 (0.80–1.04)†
MCA-PI $< 10^{th}$ percentile	362 (19.9)	20 (28.2)
CPR MoM	0.95 (0.79–1.13)	0.87 (0.71–1.07)‡
CPR ratio $< 10^{th}$ percentile	407 (22.4)	24 (33.8)†
GA at delivery (weeks)	40.2 (39.0–41.5)	40.3 (39.2–41.5)
Birth weight (g)	3490 (3120–3850)	3390 (3010–3775)
Birth weight $< 10^{th}$ percentile	325 (17.9)	16 (22.5)
Neonatal morbidity		
5-min Apgar score < 7	—	19 (26.8)
Low cord blood pH*	—	42 (59.2)
Admission to NICU > 24 h	—	28 (39.4)
Hypoxic ischemic encephalopathy	—	1 (1.4)

Data are given as median (interquartile range) or *n* (%). *Umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively. †$P < 0.05$. ‡$P < 0.01$. CPR, cerebroplacental ratio; CS, Cesarean section; GA, gestational age; GH, gestational hypertension; MCA, middle cerebral artery; MoM, multiples of the median; NICU, neonatal intensive care unit; PI, pulsatility index; UA, umbilical artery.

Table 4 Univariable and multivariable logistic regression analysis in prediction of adverse neonatal outcome using maternal and pregnancy characteristics

	Univariable analysis		*Multivariable analysis*	
Characteristic	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age – 30 (in years)	0.996 (0.956–1.036)	0.830		
Maternal weight – 88 (in kg)	1.000 (0.988–1.013)	0.965		
Maternal height – 1.64 (in m)	0.985 (0.949–1.023)	0.439		
Cigarette smoker	0.941 (0.462–1.919)	0.868		
Racial origin				
Caucasian	1.000 (reference)			
Afro-Caribbean	1.302 (0.397–4.264)	0.663		
South Asian	1.479 (0.580–3.770)	0.412		
East Asian	—	—		
Mixed	—	—		
Conception				
Spontaneous	1.000 (reference)			
Assisted	1.408 (0.500–3.964)	0.517		
Parity		0.022		
Nulliparous	1.000 (reference)			
Parous, previous CS	0.810 (0.315–2.084)	0.662		
Parous, no previous CS	0.480 (0.285–0.808)	0.006	0.550 (0.344–0.880)	0.013
Medical disorder				
Chronic hypertension	—	—		
Pre-existing diabetes mellitus	1.223 (0.162–9.223)	0.845		
Pregnancy complication				
Gestational diabetes	0.823 (0.295–2.295)	0.710		
Obstetric cholestasis	0.911 (0.281–2.956)	0.877		
Gestational hypertension	2.014 (0.607–6.679)	0.253		
Pre-eclampsia	0.728 (0.098–5.392)	0.756		
Amniotic fluid volume				
Normal	1.000 (reference)			
Oligohydramnios	1.794 (0.701–4.593)	0.223		
Polyhydramnios	1.106 (0.339–3.608)	0.867		
Fetoplacental Doppler				
Umbilical artery PI MoM	2.831 (0.909–8.816)	0.073		
Middle cerebral artery PI MoM	0.250 (0.077–0.813)	0.021		
Cerebroplacental ratio MoM	0.278 (0.108–0.714)	0.008	0.301 (0.117–0.773)	0.008
Birth-weight Z-score	0.869 (0.738–1.024)	0.094		
GA at delivery – 40 (in weeks)	0.967 (0.822–1.137)	0.686		

CS, Cesarean section; GA, gestational age; MoM, multiples of the median; OR, odds ratio; PI, pulsatility index.

The CPR was $< 10^{th}$ percentile in 31.3% (5 of 16) of SGA neonates with adverse neonatal outcome and in 34.2% (111 of 325) of those without ($P = 0.811$). In the non-SGA neonates, the CPR was $< 10^{th}$ percentile in 34.5% (19 of 55) of those with adverse neonatal outcome and in 19.8% (296 of 1494) of those without ($P = 0.008$).

DISCUSSION

Principal findings

The findings of this study of induction of labor demonstrate that about 80% of pregnancies requiring Cesarean section for fetal distress in labor and those with adverse neonatal outcome deliver an AGA neonate. Consequently, if a major contributor to these adverse events is impaired placentation, the vast majority of such impairment is observed in association with AGA fetuses.

This study has also shown that there is a significant association between adverse perinatal outcome and CPR. This is not surprising because redistribution in the fetal circulation, with preferential blood flow to the brain at the expense of the viscera, has been demonstrated by cordocentesis to be associated with fetal hypoxemia and acidemia in both SGA and AGA fetuses[1–4,20]. However, the performance of CPR in screening for adverse perinatal outcome is poor, even when the assessment is carried out within 24 h prior to delivery.

A combination of maternal and pregnancy characteristics, including age, weight, racial origin, obstetric history, pre-eclampsia, gestational age at delivery and amniotic fluid volume, identified about 40% of pregnancies requiring Cesarean section for fetal distress, at FPR of 10%, and this performance of screening was not improved by addition of CPR. In screening by CPR $< 10^{th}$ percentile, the DR of Cesarean section for fetal distress was 51% at FPR of 30% in SGA neonates, and the respective

values for non-SGA neonates were 24% and 20%. In the case of adverse neonatal outcome, the CPR was < 10th percentile in 31% of SGA neonates at FPR of 34% and the respective values for non-SGA neonates were 35% and 20%.

Strengths and limitations

The strengths of our study are, first, examination of a large number of pregnancies within 24 h prior to induction of labor, second, inclusion of a consecutive series of pregnancies undergoing induction of labor at term without exclusions, according to fetal size or pregnancy complication so that the results can be generalizable, third, measurement of MCA-PI and UA-PI by appropriately trained doctors and, fourth, use of a wide range of well-accepted indicators for adverse perinatal outcome.

The main limitation of this and previous studies is the use of Cesarean section for fetal distress and adverse neonatal outcome as surrogate markers of prelabor fetal hypoxia. It is therefore uncertain whether the poor performance of CPR in the prediction of these adverse outcomes is a reflection that CPR provides poor assessment of fetal oxygenation or that the contribution of maternal and pregnancy characteristics as well as events in labor play a much greater role than prelabor fetal oxygenation in the development of fetal distress in labor or adverse neonatal outcome.

Another limitation of the study is that pregnancies undergoing induction of labor at term were preselected because, in some cases of SGA fetuses with abnormal Doppler results, elective delivery by Cesarean section would have been carried out; had induction of labor been undertaken is such cases it is likely that some would have ended up with Cesarean section for fetal distress and asphyxia at birth reflected in low Apgar score, low cord blood pH and admission to NICU. Consequently, the performance of screening by CPR for adverse perinatal outcome in SGA fetuses would have been negatively biased.

Comparison with findings from previous studies

The results of this study are similar to those of our previous studies reporting on clinical utility of CPR measured at 32 and 36 weeks' gestation, which demonstrate that the performance of screening by CPR in prediction of adverse perinatal outcome is poor, with DR ranging from about 5 to 15% at FPR of about 5%[13,14].

Two previous studies examined the value of CPR in predicting adverse outcome in pregnancies undergoing induction of labor at ≥ 37 weeks' gestation. One study examined 164 women with a SGA fetus and reported that the DR and FPR of preinduction CPR < 5th percentile were, respectively, 70% and 46% for Cesarean section for fetal distress and 66% and 40% for adverse neonatal outcome[21]. Another study in 151 AGA fetuses reported that the preinduction CPR was not significantly different between those with operative delivery for intrapartum fetal compromise or UA blood pH < 7.0 and those with normal outcome; moreover, there was no significant association between CPR and cord blood pH[22].

Implications for clinical practice

There are two potential benefits of measuring fetal CPR in a preinduction of labor clinic. First, to identify pregnancies that are at high risk of developing fetal distress in labor or an adverse neonatal outcome as a result of labor induction, that are better managed by elective Cesarean section. Second, to stratify the intensity of monitoring during labor, with high intensity for those with low CPR and low intensity for those with normal CPR. However, the poor performance of screening by CPR precludes any useful role in achieving either of these objectives.

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Appendix VII: Full text of my article "Prediction of adverse perinatal outcomes by serum placental growth factor and soluble fms-like tyrosine kinase in women undergoing induction of labour" published in Ultrasound in Obstetrics & Gynaecology.

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Prediction of adverse perinatal outcome by serum placental growth factor and soluble fms-like tyrosine kinase-1 in women undergoing induction of labor

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KEYWORDS: adverse perinatal outcome; cerebroplacental ratio; Doppler ultrasound; induction of labor; serum PlGF; sFlt-1

CONTRIBUTION

What are the novel findings of this work?
Serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of Cesarean section for suspected fetal compromise in labor or surrogate markers of adverse perinatal outcome.

What are the clinical implications of this work?
Measurement of serum PlGF and sFlt-1 is unlikely to be clinically useful in pregnancies undergoing induction of labor.

ABSTRACT

Objective *To investigate the additive value of serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), measured within 24 h prior to induction of labor, to the performance of screening for adverse perinatal outcome provided by maternal risk factors and the cerebroplacental ratio (CPR).*

Methods *This was a prospective observational study of 795 singleton pregnancies undergoing induction of labor at ≥ 37 weeks' gestation. Before induction of labor, Doppler ultrasound was used to measure the pulsatility index (PI) in the umbilical artery (UA) and fetal middle cerebral artery (MCA) and maternal blood was obtained for measurement of serum PlGF and sFlt-1. The measured UA-PI, MCA-PI and their ratio (CPR) were converted to multiples of the median (MoM) after adjustment for gestational age, and the measured PlGF and sFlt-1 were converted to MoM after adjustment for gestational age, maternal characteristics and the machine used for the assays. Univariable and multivariable logistic regression analysis was used to determine factors that provided a significant contribution in the prediction of adverse perinatal outcome, defined as the presence of any one of Cesarean section for non-reassuring fetal status in labor, umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7 or admission to the neonatal intensive care unit for ≥ 24 h. The detection rate (DR) and false-positive rate (FPR) in screening for adverse perinatal outcome were determined.*

Results *In pregnancies with adverse perinatal outcome, compared to those without, median serum PlGF MoM was lower (0.44; interquartile range (IQR), 0.30–0.82 vs 0.60; IQR, 0.36–1.07; P = 0.003), but median sFlt-1 MoM was not significantly different (P = 0.080). Multivariable regression analysis demonstrated that, in the prediction of adverse perinatal outcome, there was significant contribution from maternal risk factors and CPR MoM but not PlGF MoM or sFlt-1 MoM. The performance of screening for adverse perinatal outcome achieved by maternal risk factors alone (DR of 28.9% at FPR of 10%) was not improved by the addition of CPR (DR of 33.8% at FPR of 10%) (area under the curve, 0.702; 95% CI, 0.654–0.750 vs 0.712; 95% CI, 0.664–0.760; P = 0.233).*

Conclusion *Serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of adverse perinatal outcome.*

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ORIGINAL PAPER

INTRODUCTION

In women at term, impaired placentation and fetal hypoxemia, reflected in low serum levels of the angiogenic placental growth factor (PlGF), high levels of the antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and reduced cerebroplacental ratio (CPR), are associated with increased risk of adverse perinatal outcome in both small-for-gestational-age (SGA) and non-SGA fetuses[1–7].

Such associations raised the possibility that serum biomarkers of impaired placentation could provide clinically useful information in the prediction and prevention of adverse perinatal outcome. However, studies have reported contradictory results concerning the performance of biomarkers for prediction of adverse outcome, which could at least in part be attributed to different intervals between assessment and delivery. In order to overcome this problem, we decided to investigate the potential value of biomarkers measured within 24 h prior to induction of labor at term. In a previous study of 1902 women with a singleton pregnancy undergoing induction of labor at ≥ 37 weeks' gestation, we found that low CPR was associated with increased risk of Cesarean section for non-reassuring fetal status in labor and adverse neonatal outcome, but the performance of CPR for such surrogates of adverse perinatal outcome was poor[7].

The objective of this study was to investigate the additive value of serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, to the performance of screening for adverse perinatal outcome provided by maternal risk factors and CPR.

METHODS

Study population

This was a prospective observational study for prediction of adverse pregnancy outcome following induction of labor at Medway Maritime Hospital, UK between July 2016 and August 2017. At this hospital, women booked for induction of labor attend the preinduction clinic within 24 h prior to administration of the induction agent. At this appointment, we recorded maternal characteristics and medical and obstetric histories, and performed an ultrasound scan to, first, determine presentation, second, estimate fetal weight from measurements of fetal head circumference, abdominal circumference and femur length[8,9] and, third, carry out a transabdominal color Doppler examination for measurement of umbilical artery (UA) pulsatility index (PI) and fetal middle cerebral artery (MCA) PI[10]. Maternal blood was obtained and stored at −80 °C for subsequent biochemical analysis of PlGF and sFlt-1 (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined from the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[11,12].

We included singleton pregnancies that were booked for induction of labor at ≥ 37 weeks' gestation and delivering a phenotypically normal neonate, for which there were available measurements of maternal serum PlGF and sFlt-1. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by London-Dulwich Research Ethics Committee (REC reference 16/LO/0367).

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (white, black, South Asian, East Asian or mixed), method of conception (spontaneous or assisted by use of ovulation induction drugs or *in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension or diabetes mellitus, obstetric complications such as obstetric cholestasis, gestational diabetes mellitus, gestational hypertension or pre-eclampsia, and obstetric history (nulliparous if no previous pregnancies at ≥ 24 weeks or parous, with or without history of Cesarean section). Maternal weight and height were measured and body mass index was calculated.

Indications for induction of labor

The indications for induction of labor were postdates ($n = 256$), maternal request ($n = 94$), diabetes mellitus or gestational diabetes ($n = 74$), obstetric cholestasis ($n = 41$), chronic hypertension, pre-eclampsia or gestational hypertension ($n = 33$), suspected SGA fetus ($n = 106$), reduced fetal movements ($n = 88$), suspected large-for-gestational-age fetus ($n = 31$), spontaneous prelabor rupture of membranes ($n = 42$), polyhydramnios ($n = 16$), maternal medical condition such as cardiac disease ($n = 11$), or antepartum hemorrhage ($n = 3$).

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records. We obtained data for gestational age at delivery, mode of delivery (vaginal or Cesarean section), indication for Cesarean section, birth weight, 5-min Apgar score, umbilical arterial or venous pH and details of admission to the neonatal intensive care unit (NICU).

Adverse perinatal outcome was defined as the presence of any one of Cesarean section for non-reassuring fetal status in labor (evidence of a non-reassuring fetal heart-rate pattern, a STAN event on fetal electrocardiogram analysis or fetal scalp pH < 7.1), umbilical arterial or venous cord blood pH ≤ 7 and ≤ 7.1, respectively, 5-min Apgar score < 7 or admission to NICU for ≥ 24 h.

Statistical analysis

Data were expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Mann–Whitney *U*-test and χ^2 test or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

Univariable and multivariable logistic regression analysis was carried out to determine which of the factors from maternal or pregnancy characteristics, measurements of fetoplacental Dopplers and maternal serum PlGF and sFlt-1 provided a significant contribution in the prediction of adverse perinatal outcome. Prior to the regression analysis, the continuous variables, such as age, weight and height, were centered by subtracting the arithmetic mean from each value. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. The measured UA-PI, MCA-PI and their ratio (CPR) were converted to multiples of the median (MoM) after adjustment for gestational age, and the measured PlGF and sFlt-1 were converted to MoM after adjustment for gestational age, maternal characteristics and the machine used for the assays[10,13,14]. Birth-weight *Z*-score was derived from the normal range for gestational age[9]. We estimated cut-offs for 10th and 90th percentiles for UA-PI, MCA-PI, CPR, PlGF and sFlt-1 and determined the prevalence of abnormal biomarker values in the outcome groups. Predicted probabilities from logistic regression analysis were used to construct receiver–operating characteristics curves to assess the performance of screening for adverse perinatal outcome[15].

The statistical package SPSS version 24.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

During the study period, there were 795 women udergoing induction of labor who met the inclusion criteria. There were 653 (82.1%) pregnancies without and 142 (17.9%) with adverse perinatal outcome, including 114 (80.3%) with emergency Cesarean section for non-reassuring fetal status in labor and 34 (23.9%) with abnormal umbilical cord pH, low Apgar score or admission to NICU for ≥ 24 h.

Adverse perinatal outcome

The maternal and pregnancy characteristics of those with adverse neonatal outcome are compared to those without such outcome in Table 1. In pregnancies with adverse perinatal outcome, compared to those without, there was a higher prevalence of women of black racial origin, a lower incidence of cigarette smokers and parous women without previous Cesarean section, and lower median MCA-PI MoM and CPR MoM. In pregnancies with adverse perinatal outcome, compared to those without, median serum PlGF MoM was lower (0.44; IQR, 0.30–0.82 *vs* 0.60; IQR, 0.36–1.07; $P = 0.003$), but median sFlt-1 MoM was not significantly different ($P = 0.080$) (Figure 1).

Univariable regression analysis demonstrated that, in prediction of adverse perinatal outcome, there was a significant contribution from black racial origin, being parous without previous Cesarean section, UA-PI MoM, MCA-PI MoM, CPR MoM and PlGF MoM (Table 2). Multivariable regression analysis demonstrated that, in prediction of adverse perinatal outcome, there was a significant contribution from maternal age, black racial origin, being parous without previous Cesarean section, developing pre-eclampsia and CPR MoM ($R^2 = 0.146$; $P < 0.001$) but not PlGF MoM ($P = 0.214$) or sFlt-1 MoM ($P = 0.714$) (Table 2). The performance of screening by maternal risk factors alone in prediction of adverse perinatal outcome (detection rate (DR) of 28.9% at false-positive rate (FPR) of 10%) was not improved by the addition of CPR (DR of 33.8% at FPR of 10%) (area under the curve, 0.702; 95% CI, 0.654–0.750 *vs* 0.712; 95% CI, 0.664–0.760; $P = 0.233$).

Table 1 Maternal and pregnancy characteristics in pregnancies with and those without adverse perinatal outcome

Characteristic	*No adverse outcome (n = 653)*	*Adverse outcome (n = 142)*
Maternal age (years)	28.6 (24.6–32.6)	29.5 (25.6–33.6)
Maternal BMI (kg/m^2)	31.5 (27.5–35.8)	31.9 (27.8–36.7)
Cigarette smoker	96 (14.7)	12 (8.5)*
Racial origin		
White	604 (92.5)	127 (89.4)
Black	11 (1.7)	9 (6.3)**
South Asian	27 (4.1)	5 (3.5)
East Asian	5 (0.8)	0 (0)
Mixed	6 (0.9)	1 (0.7)
Conception		
Spontaneous	632 (96.8)	133 (93.7)
Assisted	21 (3.2)	9 (6.3)
Obstetric history		
Nulliparous	279 (42.7)	95 (66.9)
Parous, previous CS	31 (4.7)	16 (11.3)**
Parous, no previous CS	343 (52.5)	31 (21.8)**
Pregnancy complication		
Gestational diabetes	50 (7.7)	13 (9.2)
Obstetric cholestasis	35 (5.4)	7 (4.9)
GH	16 (2.5)	5 (3.5)
Pre-eclampsia	7 (1.1)	4 (2.8)
Fetoplacental biomarkers		
UA-PI MoM	1.00 (0.89–1.14)	1.06 (0.90–1.17)
UA-PI > 90th percentile	106 (16.2)	29 (20.4)
MCA-PI MoM	0.97 (0.84–1.12)	0.95 (0.81–1.05)*
MCA-PI < 10th percentile	137 (21.0)	40 (28.2)
CPR MoM	0.97 (0.80–1.14)	0.89 (0.72–1.12)**
CPR < 10th percentile	143 (21.9)	40 (28.2)
PlGF MoM	0.60 (0.36–1.07)	0.44 (0.30–0.82)**
PlGF < 10th percentile	305 (46.7)	84 (59.2)**
sFlt-1 MoM	1.19 (0.85–1.79)	1.31 (0.91–2.14)
sFlt-1 > 90th percentile	166 (25.4)	47 (33.1)
GA at delivery (weeks)	40.1 (39.0–41.4)	40.2 (39.2–41.5)
Birth weight (g)	3470 (3097–3820)	3495 (3010–3882)
Birth weight < 10th percentile	124 (19.0)	35 (24.6)

Data are given as median (interquartile range) or *n* (%). *$P < 0.05$. **$P < 0.01$. BMI, body mass index; CPR, cerebroplacental ratio; CS, Cesarean section; GA, gestational age; GH, gestational hypertension; MCA, fetal middle cerebral artery; MoM, multiples of the median; PI, pulsatility index; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UA, umbilical artery.

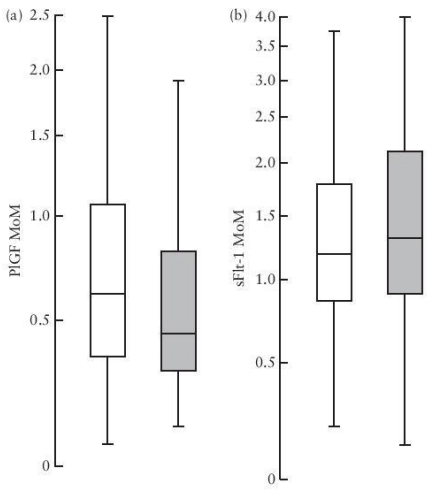

Figure 1 Box-and-whiskers plots of maternal serum placental growth factor (PlGF) multiples of the median (MoM) (a) and soluble fms-like tyrosine kinase-1 (sFlt-1) MoM (b) in pregnancies with (■) and those without (□) adverse perinatal outcome. Difference between groups was significant for PlGF MoM ($P = 0.003$) but not for sFlt-1 MoM ($P = 0.080$). Boxes are median and interquartile range, and whiskers are range.

DISCUSSION

Principal findings

The main findings of this study of induction of labor at term are, first, adverse perinatal outcome occurred in 18% of cases, second, in pregnancies with adverse perinatal outcome, compared to those without, there was lower median MCA-PI MoM, CPR MoM and serum PlGF MoM, but sFlt-1 MoM was not significantly different, third, multivariable regression analysis demonstrated that the risk of adverse perinatal outcome increased with increasing maternal age and decreasing CPR, was higher in women of black racial origin than in white women and in those with pre-eclampsia, and was lower in parous women without previous Cesarean section than in nulliparous women, and, fourth, the performance of screening for adverse perinatal outcome by maternal risk factors, with DR of 29% at FPR of 10%, was not improved by the addition of any of the biomarkers of impaired placentation and fetal hypoxemia.

These findings suggest that, first, low PlGF and CPR and high sFlt-1 provide poor prediction of impaired placentation and fetal oxygenation or, second, the contribution of maternal and pregnancy characteristics as well as events in labor play a much greater role than does impaired placentation in the development of fetal compromise in labor or adverse neonatal outcome. Alternatively, the selected outcomes of Cesarean section for non-reassuring fetal status in labor, low 5-min Apgar score, low cord

Table 2 Univariable and multivariable logistic regression analysis in prediction of adverse perinatal outcome by maternal and pregnancy characteristics

	Univariable analysis		*Multivariable analysis*	
Characteristic	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age – 30 (in years)	1.030 (0.999–1.063)	0.062	1.053 (1.018–1.088)	0.002
Maternal body mass index – 32 (in kg/m^2)	1.017 (0.988–1.047)	0.246	—	—
Cigarette smoker	0.536 (0.285–1.005)	0.052	—	—
Racial origin				
White	1.000 (reference)			
Black	3.891 (1.580–9.585)	0.003	4.589 (1.730–12.175)	0.002
South Asian	0.881 (0.333–2.331)	0.798	—	—
Mixed	0.793 (0.095–6.641)	0.830	—	—
Assisted conception	2.037 (0.912–4.546)	0.083	—	—
Obstetric history				
Nulliparous	1.000 (reference)			
Parous, previous CS	1.516 (0.794–2.894)	0.207	—	—
Parous, no previous CS	0.265 (0.172–0.410)	< 0.001	0.216 (0.138–0.339)	< 0.001
Pregnancy complication				
Gestational diabetes	1.215 (0.641–2.303)	0.550	—	—
Obstetric cholestasis	0.916 (0.398–2.105)	0.835	—	—
Gestational hypertension	1.453 (0.523–4.034)	0.473	—	—
Pre-eclampsia	2.675 (0.772–9.263)	0.121	3.874 (1.037–14.478)	0.044
Fetoplacental biomarkers				
Umbilical artery PI MoM	2.543 (1.016–6.364)	0.040	—	—
Middle cerebral artery PI MoM	0.337 (0.130–0.876)	0.026	—	—
Cerebroplacental ratio MoM	0.343 (0.162–0.729)	0.005	0.430 (0.194–0.951)	0.037
Placental growth factor MoM	0.748 (0.562–0.995)	0.046	—	—
Soluble fms-like tyrosine kinase-1 MoM	1.156 (0.973–1.374)	0.100	—	—
Birth-weight Z-score	0.905 (0.801–1.022)	0.109	—	—

CS, Cesarean section; MoM, multiples of the median; OR, odds ratio; PI, pulsatility index.

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blood pH and admission to NICU for ≥ 24 h do not reflect adequately adverse perinatal outcome.

Comparison with findings from previous studies

Previous studies examining the value of low CPR in predicting adverse outcome in pregnancies undergoing induction of labor at ≥ 37 weeks' gestation reported contradictory results[7,16,17]. A study of 19 207 women with a singleton pregnancy undergoing routine assessment at 35–37 weeks' gestation reported that serum PlGF < 5th percentile and sFlt-1 > 95th percentile were associated with increased risk of Cesarean delivery for suspected fetal compromise in labor and neonatal unit admission for ≥ 48 h; however, the performance of screening for these adverse outcomes by maternal factors and estimated fetal weight was not improved by the addition of these biochemical markers[18]. Similarly, a study of 438 pregnancies reported that, although PlGF measured at 38–40 weeks' gestation was lower in those with adverse intrapartum and neonatal outcomes than in those without adverse outcome, the performance of screening was very poor[19].

Strengths and limitations

The strengths of our study are, first, examination of a large number of pregnancies within 24 h prior to induction of labor, second, inclusion of a consecutive series of pregnancies undergoing induction of labor at term without exclusions according to fetal size or pregnancy complication so that the results may be applied widely, third, measurement of MCA-PI and UA-PI by appropriately trained doctors, fourth, measurement of sFlt-1 and PlGF by automated machines that provide reproducible results, fifth, expression of the values of the biomarkers as MoMs after adjustment for maternal factors and reagents used that affect the measurements, and, sixth, use of a wide range of well-accepted indicators of adverse perinatal outcome.

There are two limitations of this and previous similar studies. First, potential inadequacy of the surrogate markers of adverse perinatal outcome that may be affected to a greater extent by events in labor and delivery rather than by prelabor fetal oxygenation and, second, pregnancies undergoing induction of labor at term are preselected because, in some cases of SGA fetus with abnormal Doppler results, elective delivery by Cesarean section would have been carried out; consequently, the performance of screening by PlGF, sFlt-1 and CPR for adverse perinatal outcome in SGA fetuses would have been biased negatively.

Conclusions

Serum PlGF and sFlt-1, measured within 24 h prior to induction of labor, do not provide a significant additional contribution to maternal risk factors in the prediction of Cesarean section for suspected fetal compromise in labor or surrogate markers of adverse perinatal outcome. Consequently, measurement of these metabolites is unlikely to be clinically useful in pregnancies undergoing induction of labor.

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