Predicting Intrapartum Outcomes in Twin Pregnancy

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Abstract

Introduction: Multiple pregnancies affect approximately 1 in 60 pregnancies with this rate steadily increasing due to increasing maternal age and use of artificial reproductive techniques. Twin pregnancies are categorised based on the number of placentas supporting the twins with those that are monochorionic at increased risk of complications and adverse outcomes. The management of twin pregnancies from identification to delivery is vital in ensuring positive outcomes for the mother and fetuses and is highly guided by the latest clinical evidence and clinical practice guidelines. Current evidence and guidance on how to manage the delivery and intrapartum period of twin pregnancies is sparse and creates ambiguity over clinical scenarios for healthcare professionals caring for women pregnant with twins.

Methods: We performed a review of international guidelines on the management of multiple pregnancy as well as a systematic review of literature looking at induction of labour versus standard care for twin pregnancies at term. To conduct these reviews, we searched online databases and performed a hand search for guidelines. The papers and guidelines were screened and assessed for risk of bias. We carried out a retrospective cohort study of women pregnant with twins at Liverpool Women's Hospital from 2010-2020 to identify predictors of successful vaginal delivery. Data were collected from patient hospital records and analysed to develop a clinical prediction model. We conducted a further study looking at the use of computerised cardiotocography in assessing fetal wellbeing. Data for this study were collected from patient hospital records and we performed descriptive analysis.

Results: Our review of guidelines found consensus in the determination of chorionicity within the first trimester, fetal anomaly screening between 18 and 22 weeks gestation, and screening for Twin to twin transfusion syndrome (TTTS). Those that provided guidance, advised caesarean section to deliver monochorionic monoamniotic twins and epidural anaesthesia for intrapartum analgesia. There was conflict over the use of cervical length screening, timing of delivery for dichorionic twins

and circumstances for recommending vaginal delivery. Further, there was a paucity of guidance surrounding intrapartum care. Our systematic review failed to identify whether induction of labour or standard care at term for twin pregnancies had better fetal and neonatal outcomes due to a lack of evidence. Univariable and multivariable modelling in our retrospective cohort study found previous vaginal delivery (OR 3.65), increasing Bishop's score (OR 1.28) and use of epidural (OR 1.79) to be predictors of successful vaginal delivery of both twins whilst previous fertility treatment (OR 0.47) and non-cephalic presentations of either twin (Twin 1 OR 0.04, Twin 2 OR 0.57) were associated with unsuccessful vaginal delivery of both twins. We found women pregnant with twins most commonly have computerised cardiotocography assessments for reduced fetal movements and abdominal pain. Normal STVs for both twins were recorded in 98.3% (n=550) of cases, Dawes Redman criteria met for both twins in 87.8% (n=491) of cases and there were three (0.5%) cases where delivery was expedited due to an abnormal CTG.

Conclusion: We demonstrated the lack of current evidence and guidance on the management of delivery of twin pregnancies. Our retrospective cohort study addresses this and demonstrates the factors associated with increased probability of successful and unsuccessful vaginal delivery of both twins. The clinical prediction model we developed has potential to be used in clinical practice; further assessments of accuracy, validity and reliability would confirm this. Further research to investigate the safest management strategy for women pregnant with twins at terms as well as an assessment of the reliability of cCTGs to detect fetal distress and indicate the need for intervention in women pregnant with twins undergoing assessment is required.

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List of Abbreviations:

FSH – Follicle stimulating hormone

ART – Artificial reproductive techniques

PCOS – Polycystic ovary syndrome

IUI – Intrauterine insemination

IVF – Invitro fertilisation

HFEA – Human Fertilisation & Embryology Authority

DZ – Dizygotic

MZ – Monozygotic

DC – Dichorionic

MC – Monochorionic

DA – Diamniotic

MA – Monoamniotic

DCDA – Dichorionic diamniotic

MCDA – Monochorionic diamniotic

MCMA – Monochorionic monoamniotic

ISUOG – International society of Ultrasound in Obstetrics and Gynaecology

NICU – Neonatal intensive care unit

FGR – Fetal growth restriction

TTTS – Twin to twin transfusion syndrome

TAPS – Twin anaemia polycythemia sequence

FGR – Fetal growth restriction

SGA – Small for gestational age

sFGR – Selective fetal growth restriction

EFW – Estimated fetal weight

RDS – Respiratory distress syndrome

MVP – Maximum vertical pocket

MCA-PSV – Middle cerebral artery – peak systolic velocity

IUT – Intrauterine blood transfusion

OA – Occiput-anterior

OP – Occiput-posterior

OT – Occiput-transverse

ECV – External cephalic version

CTG – Cardiotocography

cCTG – Computerised cardiotocography

IV – Intravenous

FHR – Fetal heart rate

STV – Short term variation

NICE – The UK National Institute for Health and Care Excellence

TENS – Transcutaneous electrical nerve stimulation

FASP – Fetal anomaly screening programme

FIGO – The international federation of Gynaecology and Obstetrics

EFW – Estimated fetal weight

MEDC – More economically developed country

RCT – randomised control trial

ROB-II – Risk of bias tool for randomised trials

TTN – Transient tachypnoea of the new-born

PPHTN – Persistent pulmonary hypertension of the new-born

BPD – Bronchopulmonary dysplasia

HIE – Hypoxic-ischaemic encephalopathy

DR – Dawes Redman (criteria)

APGAR – New-born score

HDP – Hypertensive disorders of pregnancy

GDM – Gestational diabetes Mellitus

Chapter 1: Introduction

1.1 Definition of multiple pregnancy

A multiple pregnancy is a pregnancy in which there are two or more fetuses and occurs in approximately 1 in every 60 pregnancies (1).

1.2 Demographics of multiple pregnancy

The rate of multiple pregnancy has been steadily increasing over the last 20 years, in 1989 the multiple birth rate was 11.4 compared to 15.3 in 2019 (2). Various factors can explain this rise such as the rise in maternal age, increased demand for and development of fertility treatments (3).

In 2020 there were 8,726 births of twins or higher orders, correlating to a multiple birth rate of 14.4. This represents a slight decrease as the 5-year average from 2014-2018 was 10,728 births and a birth rate of 15.8 (2). This recent decline may be explained by the Coronavirus pandemic impacting access to fertility treatment and the collection of data.

1.2.1 Maternal Age

Over the last 30 years there has been a shift in the age at which women are having children. In 1990 the mean age at which a woman had her first child was 25.5, the latest data from 2020 shows that the current mean age is 30.7 (4). There has also been a rise in the multiple birth rate in mothers in the age ranges 40-44 and 45 and over. In 1990 the multiple birth rate for women aged 40-44 was 11.7 and 9.9 for women 45 and over, this has been rapidly increasing and now sits at 21.6 and 64.3 respectively (2).

There is an increased chance of conceiving twins and higher order gestations as maternal age increases. A 2006 study demonstrated that women over the age of 35 were more likely to have natural multiple follicle growth and multiple ovulations than women in younger age ranges. This was explained by the suggestion that declining ovarian function that occurs naturally with age leads to an increase in follicle stimulating hormone (FSH) which can cause the release of more than one egg

(oocyte) if they are mature and available (5). This natural process can partially explain the increased rates of twins in women of older maternal age, however increasing availability of fertility treatment and the decision to have children later in life cannot be forgotten.

The question of why women are having children later in life was addressed by a study looking at General Household Survey records from 1979 to 2007 (6). Trends were identified that suggest increased enrolment in education and later age of end of education in women is linked to postponement of first birth (6). A higher level of education allows those who achieve it access to a range of different employment options particularly in areas where the role would be considered a career and with a higher earning potential. But, this perpetuates the situation and further contributes to why women might wait until later in life to have children. It was also found that after a women has a child her earning potential is 20% lower than her male counterpart (7). Knowing this or at least having a vague idea on the effect that a child will have on her income or income potential it wouldn't seem illogical if a woman was to wait until later in her career to start a family.

1.2.2 Artificial Reproductive Techniques (ART)

As the age at which women decide to have children increases, so does the chance that they may struggle to conceive. Generally, a woman's fertility starts to decrease in her thirties. Around the age of 30 she will have a chance of becoming pregnancy of approximately 1.0, by 35 this will be closer to 0.6 and almost 0.0 by 40 (8, 9). Decreasing fertility is in most cases a natural process that occurs with age as the quality and quantity of oocytes lowers (10). However, in some cases there will be an explanation and cause for a couple's inability to conceive such as male factor, endometriosis or pelvic inflammatory disease (11).

The World Health Organisation defines infertility as 'the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse' (12). Around 1 in 7 couples in the UK are affected by infertility (13) and there are a range of conditions affecting both the male and female

which can cause this. In women, ovulatory disorders such as polycystic ovary syndrome (PCOS) and hypothalamic amenorrhea are the main causes but they can also be affected by fallopian tube, uterine and cervical disorders. Male infertility is the cause of infertility in 30% of couples and this primarily due to spermatogenic failure or obstructive disorders (11).

In many couples struggling to conceive there are lifestyle changes which can be made to improve fertility. These include stopping smoking, aiming for a BMI between 19-25 and reducing stress (14). If the inability to conceive persists past one year, several initial tests can be performed to highlight any issues. For the female these will be a measurement of mid-luteal phase progesterone and screening for chlamydia. The male will also be screened for chlamydia and an analysis of semen will be performed. Further, more detailed tests can be performed if required and involve ultrasound scans or more invasive diagnostic surgeries (diagnostic laparoscopy) and biopsies (14).

Treatment options for infertility range from drugs to induce ovulation such as Clomifene – an antioestrogen drug, to surgical management for tubal disorders and assisted conception treatments also known as Artificial Reproductive Techniques (ART) (14). There are various types of ART, the first is Intrauterine insemination (IUI) where good quality sperm are selected and directly injected into the uterus via a small plastic tube, hormonal treatment may also be given to stimulate ovulation. This method is commonly used for single women using a sperm donor, same sex couples or couples who need help achieving a pregnancy safely i.e. in the case of a partner being HIV positive. Another method is In vitro fertilisation (IVF), in this method mature oocytes are collected and combined with sperm for 2-3 days to allow embryos to develop, the best quality of these are then selected and inserted into the uterus via the cervix. This procedure works well for women with blocked fallopian tubes, men with abnormal sperm shape and count and people having a surrogate pregnancy. The final method is Intracytoplasmic sperm injection (ICSI), this is similar to IVF except in this procedure a single sperm is collected and injected into the oocyte via a small tube by an embryologist. The

embryo is then given time to develop and inserted into the uterus as in IVF. ICSI works well for males with a very low sperm count or erection and ejaculation issues (14, 15).

In the 1990's the rate of multiple births from IVF was approximately 28%, around 20 times higher than observed in spontaneous conception (16, 17). This was due to a lack of restrictions on the number of embryos that could be transferred during a treatment so it was common practice to transfer more than one embryo to increase the chance of a pregnancy. In 2007 the 'One at a time' campaign by the Human Fertilisation & Embryology Authority (HFEA) was launched with the aim of reducing the rate of multiple births from IVF (17). To achieve this, they set a maximum multiple birth rate of 10% and gave the freedom of how to reach this to individual clinics. The organisation has inspectors continually monitoring the outcomes of each clinic, ready to intervene and provide guidance if needed (17). Since the campaign started the multiple birth rate from IVF has been continually decreasing and the goal of 10% was achieved in 2017, the latest figures from 2019 show that the rate is now 6%.

However, ART is still a risk factor for multiple pregnancy. A recent literature review and meta-analysis looking at 38 original studies demonstrated that the rate of monozygotic twin pregnancies – where one fertilised oocyte splits in two and forms two separate embryos, is higher in women who have undergone ART than in spontaneous conception (18). Therefore, despite successful efforts to reduce the chance of multiple pregnancies from ART the natural risk of this remains prominent.

1.3 Development of a twin pregnancy

A twin pregnancy can occur in two ways, either by the fertilisation of two separate oocytes leading to dizygotic (DZ) twins or fertilisation of oocyte that splits in two - monozygotic (MZ) twins, see figure 1.

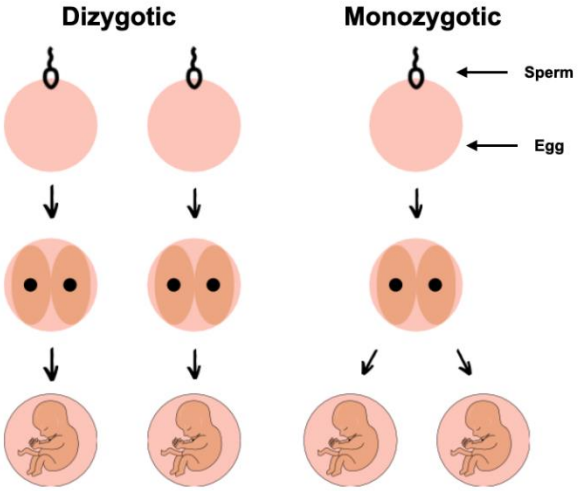

Figure 1: *Diagram displaying development of dizygotic and monozygotic twins.*

1.3.1 Chorionicity and Amnionicity

The organisation of the placenta (chorionicity) and amniotic sac (amnionicity) within the womb are two distinguishing features used to classify a multiple pregnancy.

Both the placenta and amniotic sac can either be shared by the fetuses or each fetus can have its own placenta and sac. When there are two placentas this is called dichorionic (DC) and when the placenta is shared it is known as monochorionic (MC). This is almost identical for the amniotic sac, with two sacs it is diamniotic (DA) and when there is a shared sac it is monoamniotic (MA). See figure 2.

DZ twins will always be DC and DA. However, for MZ twins there are several variations of the organisation and how these come to be are dependent on when the single fertilised egg splits into two.

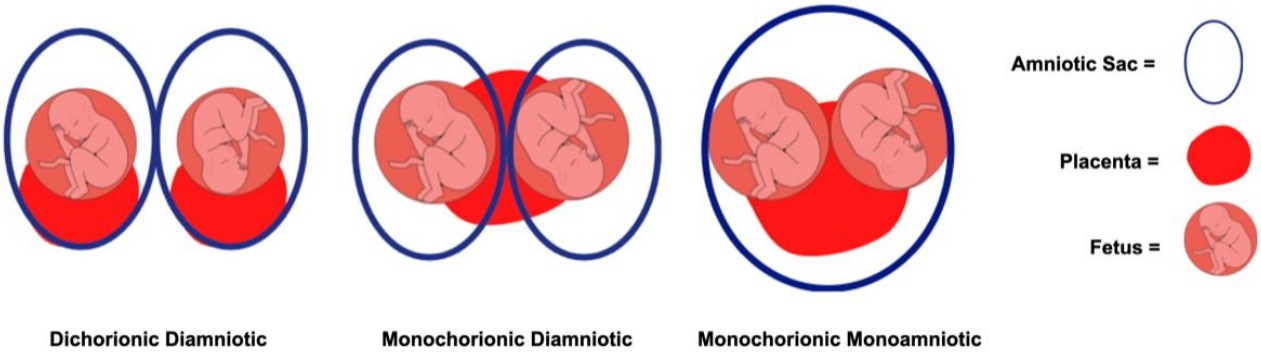

Figure 2: *Diagram outlining chorionicity and amnionicity of twin pregnancies*

If the split happens within 2-3 days of fertilisation the fetuses will go on to develop separately from one another, each with their own placenta and amniotic sac, they are known as DCDA twins. If the split occurs between 3-8 days after fertilisation there will be a shared placenta with separate sacs – MCDA. To share both a placenta and amniotic sac the split has to occur between 9-13 days after fertilisation, see figure 3.

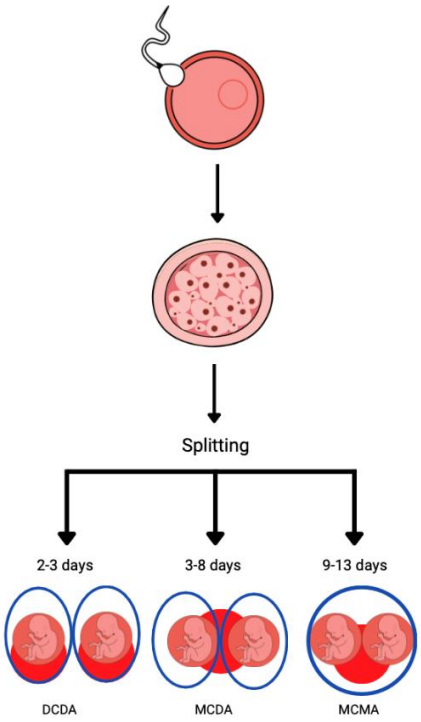

Figure 3: *Diagram of chorionicity and amnionicity by the timing of egg splitting (DCDA: dichorionic diamniotic, MCDA: monochorionic diamniotic, MCMA: monochorionic monoamniotic)*

1.3.2 Ultrasound detection of chorionicity

The determination of the chorionicity and amnionicity of a twin pregnancy is a crucial assessment in early pregnancy that provides an insight into the risks and complications that may affect the fetuses. Therefore, it is vital that this happens at the right time and is as accurate as possible. Detection of the placenta(s) and amniotic sac(s) is carried out by ultrasound; the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) states that chorionicity and amnionicity should be determined before 13+6 weeks gestation via transabdominal or transvaginal ultrasound (19). The ultrasonographer will aim to identify the number of placental masses, in a DC pregnancy where there are separate placentas these are usually identified as two individual placental masses. However, in some situations the placentas can overlap each other, making them more difficult to visualise and appear as one placenta, in this situation it is useful to visualise the amniotic membrane that covers the placenta. In DC twins the chorionic/placental tissue extends slightly between the layers of the membrane and on ultrasound is seen as the lambda (λ) sign (Figure 4.).
In MCDA twins there will be a single placental mass and the membrane will be visualised as a T-sign (figure 4.), where the thin dividing membrane stops abruptly at the edge of the placenta due to a lack of the extension of placental tissue (20).

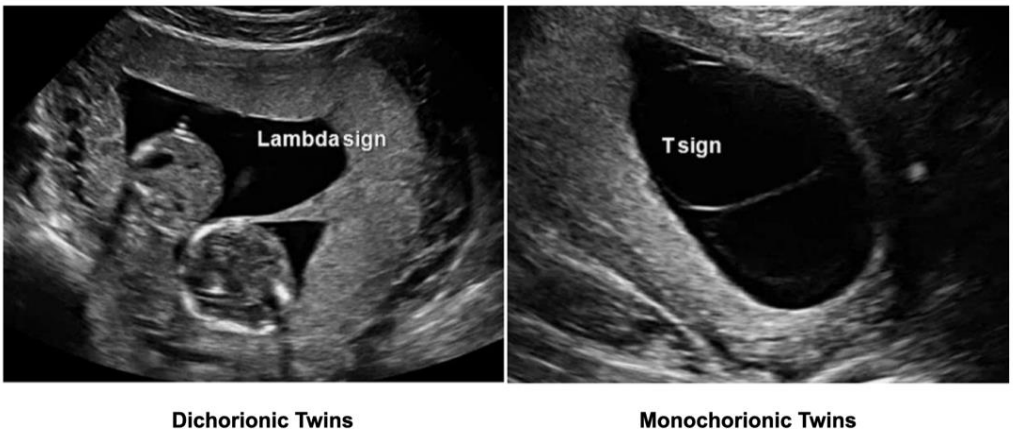

Figure 4: *Image demonstrating the Lambda-sign and T-sign as seen in DC and MC twin pregnancies adapted from ISUOG*

In MCMA twins there is again a single placental mass but also no dividing membrane due to the fetuses sharing one amniotic sac, this is best established by the use of transvaginal ultrasound.

1.3.3 Twin Labelling

ISUOG also advises labelling the twins during pregnancy so that the fetuses can be monitored individually over time. They state that the method used should be consistent and reliable and documented clearly in order to avoid confusing over which fetus is which. The methods they mention are either using the site of the fetuses as a descriptor e.g. left and right or upper and lower, or using the insertion of the umbilical cords relative to the placental edge. The last method is to use a combination of both of these, describing the fetuses in as much detail as possible, for example 'Twin A (male) is on the maternal left with an anterior placenta and marginal cord insertion' (19).

The labelling method as mentioned should be used throughout the antenatal period, however should not be used during delivery. There is a phenomenon known as 'The perinatal switch phenomenon' where the fetuses are not delivered in the order they were originally labelled. To avoid confusion, during labour and delivery the fetuses should be labelled as leading and second twin and then identified by distinguishing features thereafter if necessary. In cases where one or more fetuses has a pathology that is not visible externally and needs immediate intervention e.g. transposition of the great arteries, an ultrasound should be performed just prior to delivery and before any intervention (19).

1.4 Complications in twin pregnancies

Twin pregnancies are at greater risk of maternal and fetal complications than singleton pregnancies (21, 22). MC twins in particular can be more complex and can be uniquely affected by a set of conditions affecting the balance of blood flow to the fetuses, these conditions are associated with adverse outcomes for the fetuses (23, 24)

1.4.1 Medical problems

Obstetric risks that occur in singleton pregnancies such as pre-eclampsia and gestational diabetes are also observed more commonly in multiple pregnancies. A retrospective cohort study looking at all births at a single hospital in Hong Kong found that in comparison to singleton pregnancies the presence of each additional fetus in a multiple pregnancy increases the risk of gestational diabetes 1.80 times (25). Further to this, gestational diabetes, particularly in twin pregnancies is associated with adverse obstetric and neonatal outcomes such as risk of caesarean delivery (26), development of new onset gestational hypertension, admission to neonatal intensive care unit (NICU) and perinatal mortality (27). This picture is closely reflected when looking at pre-eclampsia in multiple pregnancy; the condition occurs more frequently than in singletons and also increases the risk of poor obstetric and neonatal outcomes (28). These include caesarean delivery, prolonged labour and fetal distress. This highlights the need to closely monitor women with a multiple pregnancy and manage them efficiently when required.

1.4.2 Congenital anomalies

Congenital anomalies, defined by WHO as 'structural or functional anomalies that occur during intrauterine life that can be identified prenatally, at birth or later in infancy (29), have a higher risk of developing in multiple pregnancies compared to singletons (30, 31). Twins are two to three times

more likely to have congenital abnormalities, most commonly seen in monozygotic twins with both twins displaying a defect (32). Discordant anomalies, where only one of the twin pair is affected can also occur; in DCDA twins there is a one in twenty-five chance, one in fifteen in MCDA twins and one in six for MCMA twins.

Congenital anomalies encompass a variety of conditions including chromosomal disorders such as Down's, Edward's and Patau's syndromes as well as structural conditions for example, congenital heart disease, cleft lip/palate and spina bifida. these conditions, often when more severe, are associated with high rates of spontaneous abortion and fetal mortality. This is often due to termination of pregnancy and stillbirth (33). If the affected fetus(es) survive, they often have long-term complications (34).

1.4.3 Fetal growth restriction (FGR)

Fetuses in a multiple pregnancy can be affected by fetal growth restriction (FGR). This is a condition in which the fetuses do not grow at the expected rate for their gender or negatively deviate from their expected growth pattern. This can lead to the fetus/neonate being small for gestational age (SGA) where their estimated weight or birth weight is less than the 10^{th} percentile for their gestational age (35). Babies born SGA are at a higher risk of being hospitalised throughout childhood and having unfavourable behavioural development than babies born appropriate for gestational age (36). FGR can affect any pregnancy, however it is seen to affect multiple pregnancies, particularly MC twins, more frequently (37) as well as SGA in twins being associated with increased risk of stillbirth (38). However, it is known that twins grow less rapidly than singletons in the third trimester and are generally smaller for gestational age in comparison to singletons (39). This therefore questions whether with the standard practice of using singleton growth charts to measure twin growth is overexaggerating the incidence of FGR and SGA in twins. Despite this, twins overall experience

greater perinatal morbidity and mortality than singletons with birth weight being a predictor of this, particularly in twins delivered before 37 weeks gestation (40).

FGR in twins is further complicated when just one twin has restricted growth and the other grows normally, this situation is known as selective fetal growth restriction (sFGR). The condition is diagnosed when one twin has an estimated fetal weight (EFW) less than the 10th centile and when there is a 25% or greater discordance of EFW between the two twins (37). The outlook for this condition depends on the severity, less severe cases have a good prognosis with few complications whereas those that are more severe are have a higher rate of intrauterine death, perinatal and neonatal morbidity (41). Management of sFGR can be complicated as any interventions will have an effect on both the healthy and sFGR fetus, therefore treatments, particularly Fetoscopic interventions, are reserved for severe cases and close surveillance is often the management strategy (37).

1.4.4 Pre-term birth

Multiple pregnancies are at high risk of preterm birth, up to six times more so than singletons (42). Pre-term birth is defined as delivery between 24 and 37 weeks gestation and can be further classified into Extremely preterm (<28 weeks gestation), Very preterm (28-32 weeks gestation) and Moderate to late preterm (32-37 weeks gestation). One study including 1436 twins observed an average gestational age of delivery of 35^{+5} weeks gestation (43). The effects of preterm birth are vast, globally it is the leading cause of death in children and accounts for 35% of deaths in the neonatal period (birth-28 days) (44). A cross-sectional study in China looking at 2651 preterm births from 2018-2020 in 107 hospitals found neonatal mortality rates to be 44.4% in extremely preterm infants, 15.8% in very preterm infants and 4.3% in all preterm births. The morbidities that were most frequently observed included hyperbilirubinemia, pneumonia/sepsis, respiratory distress syndrome (RDS) and intraventricular haemorrhage (45). There are many causes for pre-term birth, in the case

of twins it is often medically induced and due to elective induction or caesarean section before term to reduce the chance of stillbirth of which there is an overwhelming risk in multiple pregnancy compared to singletons (38, 46, 47). However, a high proportion of multiple pregnancies will go into spontaneous pre-term labour (48). Various methods to predict and prevent this have been suggested including cervical length screening, cervical pessary and vaginal progesterone however none of these have been implemented in standard UK practice (49).

1.4.5 Monochorionic complications

Monochorionic twins share a single placenta and therefore share the blood supply that is provided through this. Within the placental mass there are many blood vessels which deliver oxygen and vital nutrients to each of the twins. Due to the nature of a shared placenta connections between these blood vessels, known as vascular anastomoses, will arise. There are three types of anastomoses that can form, venous-venous, arterial-arterial and arterial-venous as shown in figure 5.

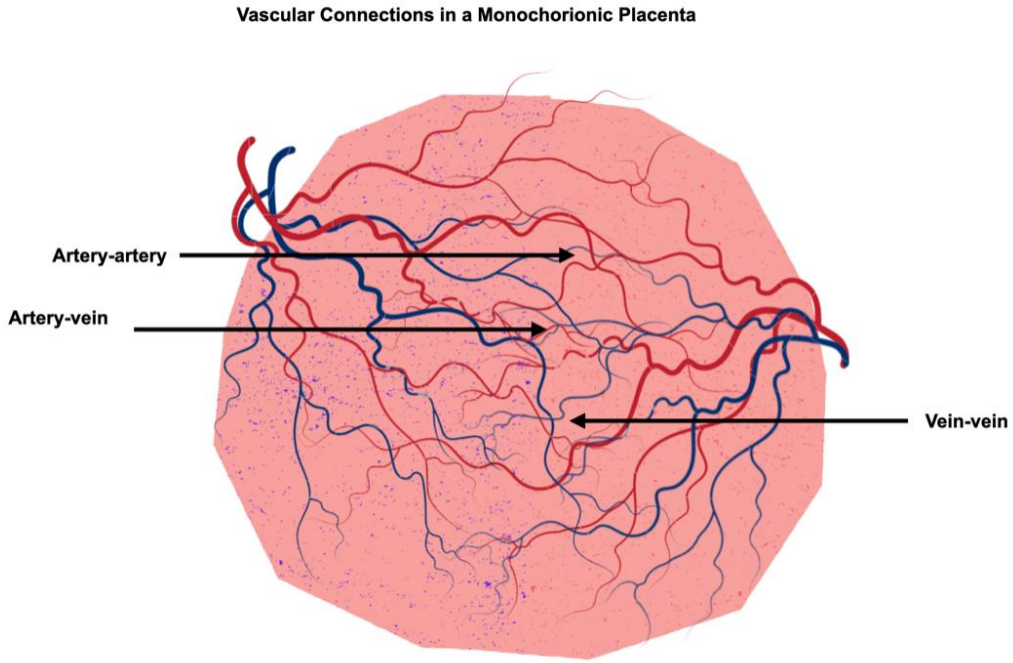

Figure 5: *Diagram outlining the vascular anastomoses that can arise in a monochrionic placenta*

The last two are implicated in conditions affecting MCDA pregnancies. Arterial-venous connections allow a flow of blood from one twin to the other at a rate that is greater than the rate of growth of the receiving twin and are often observed in placentas affected by Twin to Twin Transfusion Syndrome (TTTS) (50). However, this can be compensated by the presence of arterial-arterial anastomoses which have been seen to be present in placentas unaffected by TTTS and absent in those that are affected (51, 52).

1.4.5.1 Twin to Twin Transfusion Syndrome (TTTS)

By definition TTTS is 'a disease derived from the unbalanced sharing of blood between fetuses via placental anastomosing vessels' (53) and this affects approximately 15% of MCDA twins (54). The fetus that receives a smaller share of the blood is known as the donor and is likely to develop anaemia, have a decreased volume of amniotic fluid know as oligohydramnios and be affected by FGR. The fetus receiving a greater share of the blood is known as the recipient and will experience opposite effects to the donor. These include cardiac failure, polycythemia – high levels of haemoglobin concentration, and excess amniotic fluid – polyhydramnios (54).

TTTS is diagnosed most frequently in the second trimester. There are two features which need to be present for a formal diagnosis; 1) the pregnancy must be MCDA and 2) there must be oligohydramnios (maximum vertical pocket (MVP) of <2cm) in one sac and polyhydramnios (MVP >8cm) in the other (55).

TTTS can present with varying severity and this has been classified into stages known as The Quintero Staging System (56). This uses features observed on ultrasound such as volume of amniotic fluid (MVP), absence of bladder visualisation, abnormal Doppler findings (absent or reversed end-

diastolic velocity in the umbilical artery, absent or reversed flow in the ductus venosus, or pulsatile umbilical venous flow), hydrops and fetal demise (53). The stages range from I to V and can be seen in figure 6.

Stage I	Discordant amniotic fluid volume, bladder of donor twin still visible on ultrasound
Stage II	Criteria of stage I, but urine not visible in donor twin's bladder
Stage III	Criteria of stage II and abnormal doppler studies of umbilical artery, umbilical vein or ductus venosus
Stage IV	Ascites or frank hydrops in either twin
Stage V	Fetal demise of either twin

Figure 6: *The Quintero Stages of TTTS*

TTTS accounts for around 17% of perinatal mortality in twins and approximately 50% of all perinatal deaths in MCDA twins (55, 57). The outcomes of TTTS are highly dependent on the severity of the disease. Without treatment cases of TTTS stage I are likely to remain stable or become less severe 75% of the time. However in untreated TTTS cases considered advanced (≥ stage III) the rate of perinatal loss is between 70-100% (55). Twins that survive TTTS are unlikely to do so without complication, premature birth is common and the twins are likely to be affected by prematurity associated conditions e.g. RDS & chronic lung disease. Furthermore, fetuses with TTTS are at a greater risk of cerebral injury and neurologic conditions, congenital heart disease, cardiovascular morbidity and renal complications (58).

Management for TTTS includes two treatments, Amnioreduction and Fetoscopic Laser Photocoagulation. In Amnioreduction excess amniotic fluid causing polyhydramnios in the recipient twin is removed by inserting a needle through the uterus into the amniotic sac via ultrasound guidance. The fluid is drained through a plastic tube into a sterile bag where the volume and

amniotic pressure within the amniotic sac is then measured (59). The procedure for Fetoscopic Laser Photocoagulation involves inserting a fetoscope and laser percutaneously into the uterus and amniotic sac via ultrasound guidance. The laser is then used to ablate the inter-twin anastomoses, preventing further unequal blood distribution and lessening the complications of TTTS (60). The Laser ablation procedure however is risky in nature; there is a risk of pre-term rupture of membranes, pre-term delivery, placental abruptions and chorioamnionitis (55). Women intending to undergo this procedure should be counselled on this.

The 2004 Eurofetus trial which compared endoscopic laser coagulation with serial Amnioreduction as treatments for TTTS found that with laser treatment the survival of at least one twin to 28 days of age was 20% higher than amnioreduction as well as a reduction in the risk of neurologic complications at six months of age (61). Guidance from ISUOG summarises current evidence on both treatments, stating Laser ablation as the 'treatment of choice' for Quintero stages II and above (19). For stage I TTTS cases close surveillance and amnioreduction are the advised treatments with a criterion for escalation to laser treatment given. This criteria includes shortening of cervical length, worsening polyhydramnios and maternal discomfort (19).

1.4.5.2 Twin anaemia polycythemia sequence (TAPS)

Another condition that can affect MC twins and arises due to unequal blood flow between the fetuses is Twin anaemia polycythemia sequence (TAPS). The condition itself is similar to TTTS however the discordance in amniotic fluid volumes seen in TTTS is not present in TAPS. The fetuses are affected by major differences in haemoglobin levels with the donor twin becoming anaemic and the recipient developing polycythemia (62).

TAPS occurs spontaneously in MC twins in around 5% of cases and also develops in 2%-16% of TTTS cases treated by Fetoscopic laser photocoagulation. This occurs if the treatment is incomplete, causing there to be remaining anastomoses (63). TAPS can develop between 15-35 weeks gestation and is diagnosed on ultrasound with discordant MCA-PSV (middle cerebral artery – peak systolic velocity) doppler measurements, in the recipient there will be decreased velocity, indicating polycythemia and in increased velocity in the donor suggesting anaemia (63).

In twins affected by TAPS both fetuses are at an increased risk of perinatal mortality, however for the donor twin this risk is increased four-fold. For those that develop TAPS spontaneously the risk of spontaneous perinatal death is 9% and 18% for those that arise post laser treatment (63). There are several treatment options for TAPS with a lack of consensus on a preferred option. These include expectant management, induction of labour and pre-term delivery, intrauterine blood transfusion (IUT), selective fetocide and laser surgery (62, 63). A study of 370 cases of spontaneous and post laser TAPS by *Tolienaar et al* found no differences in perinatal mortality for any of the treatment options, however there was an observed higher rate of severe neonatal morbidity after treatment with IUT or pre-term delivery (64).

1.4.5.3 Twin reversed arterial perfusion (TRAP)

A rarer complication of monochorionicity is Twin reversed arterial perfusion (TRAP). This condition is characterised by incomplete cardiac development in one twin, the presence of vascular anastomoses within the shared placenta and a normal developed twin supplying both circulations. The underdeveloped fetus is called the ‘acardiac twin’ and the normal co-twin is known as the ‘pump twin’ (65). Due to the improved use of ultrasound diagnosis TRAPS is estimated to affect 2.6% of monozygotic twins which was previously estimated to be around 1% (65).

TRAP is a dangerous condition, despite the acardiac being incompatible with life its presence throughout the pregnancy impacts the pump twin, leading to a perinatal mortality rate between 50%-75% without intervention (66). Due to increased demand and strain put on the cardiac system of the pump twin the development of congestive heart failure and polyhydramnios is common, this consequently leads to a risk of pre-term rupture of membranes due to uterine overdistention. The nature of the blood flow in TRAPS means that deoxygenated blood flows back to the pump twin through the vascular anastomoses and puts the fetus at risk of hypoxia and FGR (65, 67).

The management of TRAP is based around improving the survival and morbidity of the pump twin. One of the main treatments is Cord Occlusion in which the blood flow through the umbilical cord to the acardiac twin is interrupted, relieving demand and strain on the pump twin. This can be performed via monopolar or bipolar thermocoagulation as well as laser coagulation. Another method is Intrafetal Ablation in which the abdominal aorta or pelvic vessels of the acardiac twin, which are easily visualised on colour Doppler ultrasound, are ablated (65). Surgical intervention, in particular Cord Occlusion, to treat TRAP has been shown to improve perinatal survival rates up to 83% (66). However the current issues surround the ideal timing of treatment to optimise outcomes (65).

1.4.6 Monoamniotic complications

Monochorionic monoamniotic twins, that share a placenta and a single amniotic sac are rare with an estimated prevalence of 8 in every 1000 twin pregnancies (68). They are monozygotic and arise due to splitting of the oocyte between 9 and 13 days after fertilisation. Monoamniotic twins are at risk of additional complications including congenital abnormalities and cord complications (69).

Due to the delayed embryo splitting, MCMA twins are more likely to have structural congenital abnormalities ranging from cardiac defects to conjoining of the twins. These conditions, depending on the type and severity have varying outcomes and impact on the fetuses and contribute to the high level of fetal mortality and morbidity in MA twins (41, 70).

MCMA twins have a large proportion of artery-artery anastomoses within their shared placenta and are therefore more likely to develop TRAP sequence than MCDA twins, but conversely are less likely to develop TTTS (69). There is a greater risk of fetal death in MCMA twins compared to DC twins and this is often due to complications of cord entanglement. This is a classic feature of MCMA twins with the intertwining of the fetuses umbilical cords present in all cases, however, in some instances this can lead to acute hemodynamic instability due to compression of the cord (69).

1.4.7 Conjoined twins

Conjoined twins are rare, affecting approximately 1 in 50,000 pregnancies (71). They occur following the fertilisation of a single egg that splits very late, between 15-17 days post fertilisation. A diagnosis can be made from 12 weeks onwards via ultrasound where inseparable fetal bodies and a single umbilical cord are seen (71). The prognosis for conjoined twins is highly dependent on the extent of organ sharing between the twins and the likelihood of successful surgery to separate them (72)

1.5 Normal labour and delivery

1.5.1 Normal labour

Labour, the process in which the fetus(es) and placenta(s) are expelled from the uterus begins with the onset of regular, painful contractions that causes changes to the cervix so that it becomes dilated, shorter and softer (73). Labour can be split into three stages; first stage, second stage and third stage.

1.5.1.1 The first stage of labour

The first stage of labour can be subdivided into two stages; the latent phase and the active phase or established labour. The latent phase is between 0-4cm cervical dilation and can have a duration up to 20 hours in a nulliparous woman (a woman giving birth for the first time), or 14 hours in a multiparous woman (a woman who has had previous births). Established labour occurs between 5cm and full dilation (10cm), this phase is usually faster with cervical dilation occurring at a rate of 1.2-1.5cm per hour (73). Throughout the first stage of labour the head of the fetus or leading fetus will move lower into the pelvis, this is aided by uterine contractions. In established labour these will last for 40-60 seconds occurring 3-4 times in 10 minutes. The contractions cause the cervix to be pulled up against the head of the fetus, this along with the downward pressure of the head into the cervix, causes effacement (thinning of the cervix) and dilation (74, 75).

The movement of the fetus through the pelvis can be described using three terms; presentation, presenting part, position. The presentation is the part of the fetus that is most proximal to the pelvis and cervix, i.e. the head (cephalic presentation) or the buttocks (breech presentation). The presenting part is the part of the fetuses that is palpated most proximal to the cervix on vaginal examination i.e. the buttocks or feet in breech presentation or the vertex, brow or face in cephalic

presentation. The position is used to further describe cephalic presentations by describing the rotation of the head within the pelvis (74).

At the time of delivery, the bones that make up the skull of the fetus are yet to fuse together and the spaces between them are palpable as either long ridges (sutures) or wider spaces (fontanelles). Palpation and orientation of the sutures and fontanelles in vaginal examination allows determination of the position if the head (74). There are two fontanelles, an anterior (bregma) which sits above the forehead and posterior (occiput) which is towards the back of the top part of the head (figure 7).

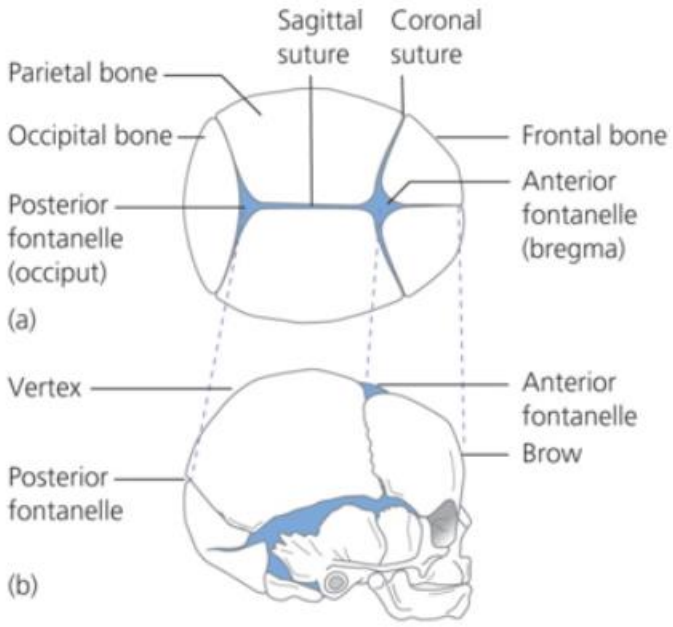

Figure 7: *Diagram showing the sutures and fontanelles in the fetal head from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

The ideal position of the head through the pelvic outlet is occiput-anterior (OA), this is where the posterior fontanelle is palpated anteriorly towards the pubic symphysis. Other positions include occiput-posterior (OP) and occiput-transverse (OT) (figure 8), these positions are still compatible

with vaginal delivery however they may require instrumental or operative intervention, particularly with OT (74).

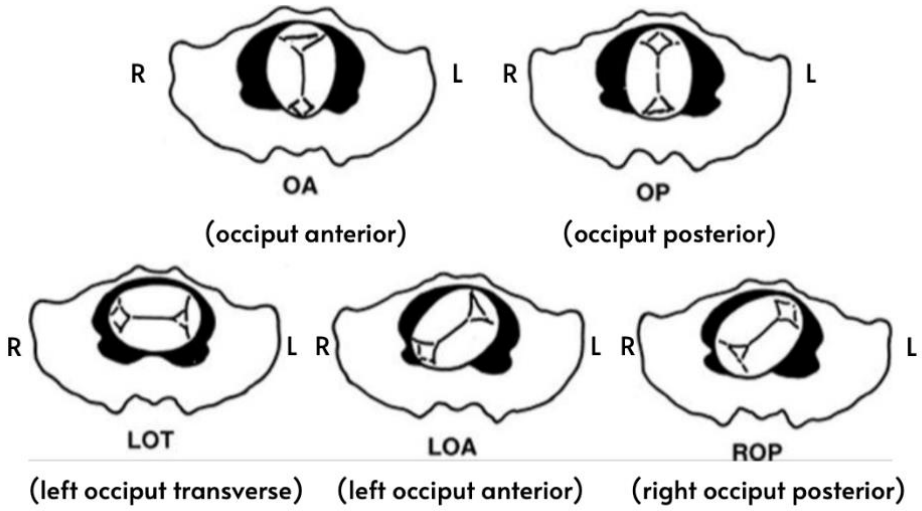

Figure 8: *Fetal positions during delivery – Image adapted from Danforth's Obstetrics and Gynaecology, 9th Edition*

1.5.1.2 The second stage of labour

The second stage of labour is reached when full cervical dilation (10cm) is achieved. In this stage the fetus descends into the birth canal and is delivered through uterine contractions, maternal effort and a series of change in fetal positions known as the cardinal movements (73). These allow the fetus to rotate within the pelvis, enabling safe delivery of the head and shoulders.

The first movement is engagement which occurs as the fetus enters the pelvis, it then descends, flexes and internally rotates 90 degrees as the fetus moves lower into the pelvis and moves to adjust to the bones of the pelvis. After rotating there is further descent of the fetus and extension of the head which continues until the head is delivered. Once this has occurred restitution takes place in which the head rotates back to its normal position with the shoulders.

As the shoulders reach the pelvic floor, external rotation occurs so that they are in an anteroposterior position allowing safe delivery. The anterior shoulder is delivered first by applying posterior traction to the fetal head, allowing the shoulder to move under the pubic arch. The posterior shoulder is then delivered by anteriorly elevating the head, this is followed by quick delivery of the rest of the body (73-75) (Figure 9).

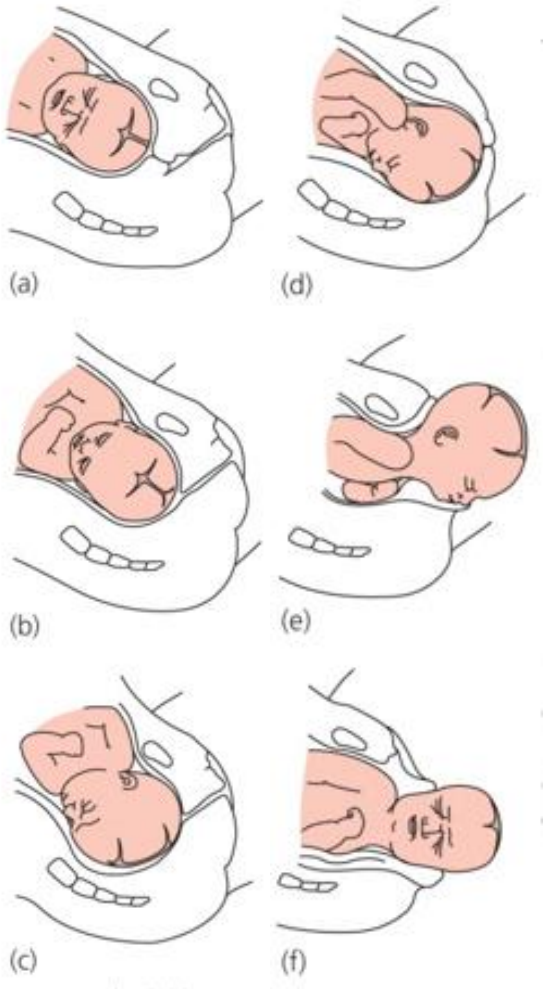

Figure 9: *The cardinal movements of labour from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

1.5.1.3 The third stage of labour

The third stage of labour occurs between the delivery of the fetus and delivery of the placenta and this should occur within 30 minutes of delivery. During this process the uterus contracts in order to separate the placenta from the uterine wall. Signs of this process beginning include lengthening of the umbilical cord and passage of bright blood. To deliver the placenta, gentle traction on the umbilical cord is applied along with suprapubic pressure to prevent uterine inversion (74, 75).

To prevent a post-partum haemorrhage, the loss of ≥500ml blood within 24 hours of delivery, active management of the third stage of labour can be used. This involves the administration of intramuscular oxytocin upon delivery of the fetal shoulders which encourages the process of uterine contraction, aiming to reduce the need for blood transfusion (76).

1.5.2 Intrapartum care

1.5.2.1 Assessment during labour

The management of the mother and fetus(es) throughout labour is crucial to ensuring a safe delivery. Observations of temperature and blood pressure should be monitored every 4 hours with maternal pulse being recorded every hour in the first stage of labour and every 15 minutes in the second stage. These measurements are taken to assess how the mother's body is coping during labour and to detect any situations that may require intervention. Pyrexia in labour – a maternal temperature of over 37.5°C is common and not always an indication of serious illness, however it is associated with adverse neonatal outcomes including admission to the neonatal intensive care unit (NICU) (77).

The progress of labour is routinely monitored by the use of a Partogram. This is a graphical record that is filled out throughout labour to determine the progression of labour (figure 10). The partogram is made up of several components including cervical dilation, descent of the head, fetal

heart rate (FHR). These measurements are taken via vaginal examination and are plotted on the graph against time, there is an 'alert' and 'action' line which if met indicates slow progress in labour and the need to consider intervention (75, 76).

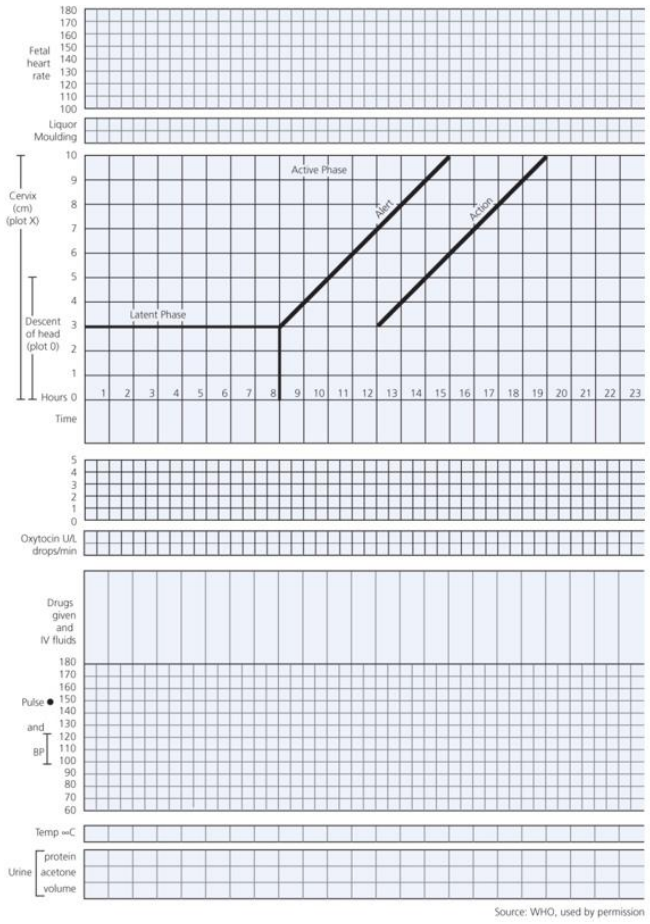

Figure 10: *A Partogram from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

1.5.2.2 Fetal Monitoring

The FHR can be measured using several methods and in low risk pregnancies this should be done every 15 minutes in the first stage of labour and every 5 minutes in the second. Either a Pinard's stethoscope or hand-held Doppler can be used, after a contraction, which is detected by manual

palpation, for 60 seconds to detect either normal or abnormal heart rate patterns. In the case of abnormal patterns, high-risk pregnancies and deterioration of condition during labour Cardiotocography (CTG) monitoring is required (75, 76). CTG allows the simultaneous and continuous monitoring of FHR and uterine contractions which is recorded and displayed either on paper or electronically. This is done by placing a pressure transducer on the anterior wall of the abdomen to detect uterine contractions as well as a doppler ultrasound transducer on the abdomen to detect the fetus(es) heart rate or an electrode clip placed on the fetal scalp during labour. Over time these measurements produce a graph which depicts the FHR in relation to contractions and when interpreted can provide an indication to condition of the fetuses. There are several features identified on a CTG, the Baseline rate which should sit between 110-160 bpm, Baseline variability which is the short-term variation (STV) in FHR which should be >5 bpm except during periods of fetal sleep, Accelerations where the FHR increases e.g. with movement and Decelerations which are decreases in FHR, normal in response to contractions but can be indicative of hypoxia or cord compression (75, 76).

1.5.2.3 Analgesia in labour

Labour is known to be a painful experience and there are a range of methods that can be used to help manage this if wanted by the mother. These include non-pharmacological, pharmacological and regional anaesthesia.

Non-pharmacological methods are often helpful in the early stages or throughout the duration of labour, they are usually inexpensive and allow the woman to maintain control that is often lost following regional anaesthesia (78). these include water immersion, massage, aromatherapy and transcutaneous electrical nerve stimulation (TENS) (75, 76, 78).

Pharmacological methods are useful for managing discomfort felt throughout labour however they can lead to adverse fetal affects in excess doses so should be careful administered (79).

Inhalational analgesia, is often the first offered pharmacological analgesia and is most commonly Entonox – a mixture of nitrous oxide and oxygen. This is administered by inhaling the gas as contractions begin and is effective for many women (75, 76, 78). Opiates are a class of analgesia that are widely used during labour, these include Pethidine, Diamorphine and Fentanyl and are administered via intra-muscular injection (75, 76, 78). These drugs have a sedative effect and can often make the mother feel confused or out of control. This effect is also observed in the fetus and neonate, leading to reduced heart rate variability, hypothermia and respiratory depression. It can take a neonate six days to fully eliminate the opioid from their system with reduced alertness and poor feeding observed in this period (78).

Regional anaesthesia is the gold standard for pain relief in labour, it is widely used and considered the most effective (76, 78). Epidural anaesthesia, the most commonly used in labour, involves placing an indwelling catheter into the lumbar epidural space between L3-L4 through which a combination of an opiate and local anaesthetic will be delivered. There will be an initial loading dose which is followed by patient controlled low-dose top-ups (75, 76, 78). Despite providing effective pain relief there are some side effects and limitations, these include hypotension, postdural headache, dural puncture and maternal fever. In addition to this due to the lack of sensation in the lower half of the body the mother will experience reduced mobility and reduced bladder sensation can lead to urinary retention (75, 76).

Other methods to induce regional anaesthesia are spinal or pudendal nerve blocks which are more commonly used in operative or instrumental deliveries. The pudendal nerve block is administered by injecting local anaesthetic bilaterally around the pudendal nerve as is passes the ischial spine. This provides, quick and effective analgesia that is required for an instrumental delivery (75, 76).

1.5.3 Complications in labour

Labour is often not a straightforward process, there are various complications that can occur throughout the duration, ranging in severity and the level of intervention required for management.

1.5.3.1 Progress in Labour

The progression of labour as mentioned previously is measured using a partogram and is assessed by vaginal examination roughly every 4 hours. If there is slow progress through the first stage of labour there are some interventions that can be used to encourage labour. If after the latent phase there is slow progression of dilation, amniotomy can be used. If slow progress persists after this in a nulliparous woman, oxytocin infusion can be administered to initiate uterine contractions. Oxytocin can also be used in multiparous women however this should be done with caution to exclude malposition or malpresentation first. In cases where full cervical dilation and second stage of labour has not been reached by 12-16 hours without any indication of imminent delivery, caesarean section should be planned for (76).

1.5.3.2 Fetal Distress

The aim of intermittent and continuous fetal monitoring is to detect fetal distress at the earliest point possible. Fetal distress is defined as 'hypoxia that has the potential to result in fetal damage or death if not reversed or the fetus is delivered urgently' (76). Fetal distress in rare cases can lead to long-term handicap but more frequently is associated with difficulties for the neonate, this includes low umbilical cord pH, the need for medical intervention and a low APGAR score – an assessment of new-born wellbeing looking at muscle tone, pulse, reflexes, skin colour and respiration (76, 80). Signs of fetal distress can be detected via CTG changes, liquor colour and fetal blood sampling. In fetuses monitored by intermittent auscultation the suspicion of fetal distress will prompt the use of CTG to get a more detailed look at the FHR. Changes seen on a CTG trace that are associated with fetal distress are variable decelerations and late decelerations. Variable decelerations will vary in timing and indicated cord compression – a common cause of hypoxia. Late decelerations are drops in the FHR the persist after the end of a contraction and indicate fetal hypoxia (76).

These changes should be taken seriously and reviewed by more than one clinician, but the clinical situation in which they are present is also important to consider. One important sign that provides an indication of the severity of the situation is the colour of liquor and presence of meconium. Meconium is the fetal bowel contents and its presence in the liquor can be worrying. If it is very diluted this is often not clinically significant but if it is undiluted and in large volumes this can be serious and is associated with increased perinatal mortality. In this scenario, CTG surveillance should be initiated if not already done. Another complication of meconium stained liquor is the risk of meconium aspiration in which the fetus aspirates its bowel contents into its lungs causing severe pneumonitis (76).

A method to confirm fetal distress and hypoxia is by taking a fetal blood scalp sample. This is done by inserting an amnioscope – a metal tube, into the vagina and cervix to visualise the scalp of the fetus. A small cut is made on the scalp and a blood sample from this is collected and sent to the laboratory for analysis of pH. If this is <7.20, indicating fetal acidosis, delivery via the fastest method should be initiated. If the pH is >7.20, close monitoring should continue to identify persistent or worsening abnormal FHR which required a further blood sample after 30 minutes (76).

Fetal distress, if not severe can be managed without immediate delivery. The mother should be placed into the left lateral position to prevent aortocaval compression, oxytocin infusions if present are to be reduced or stopped, oxygen and IV fluids can be administered and a vaginal examination to exclude cord prolapse and assess vaginal dilation can be performed (76).

1.5.3.3 Positional complications and instrumental delivery

In some cases, the fetus enters the second stage of labour in a position that is different from the ideal cephalic OA presentation. In some situations, these fetuses are delivered as normal but in others they may need additional support in the form of an instrumental delivery. This can be to rotate a malpositioned fetus or provide traction to help deliver a fetus in prolonged second stage.

This type of delivery is common with 20% of nulliparous and 2% of multiparous women needing instrumental assistance (81).

There are two main devices that are used known as Forceps and the Ventouse (figure 11). The forceps come in pairs and have a 'blade', 'shank', 'lock' and 'handle'. There are two types of forceps, rotational or non-rotational, the latter has a pelvic and cephalic curve to the blade can only be used on a fetus in an OA position. Whereas rotational forceps have a cephalic curve but only a very shallow pelvic curve which allows rotation of a malpositioned fetal head into the OA position before applying traction to aid delivery (82).

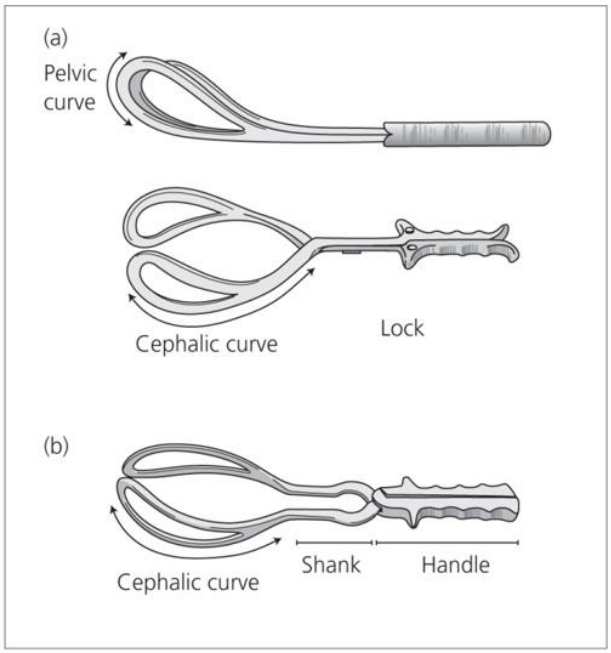

Figure 11: *Non-rotational (a) and Rotational (b) forceps from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

The second device is the Ventouse, this device has a cap that can be made from metal, rubber or plastic connected to a handle (figure 12). To operate the ventouse the cap is fixed to the fetal occiput and by applying traction during maternal pushing using the handle the fetal head can be

delivered. This can be used on an OA positioned fetus in delayed second stage of labour or to rotate and deliver a malpositioned fetus (82).

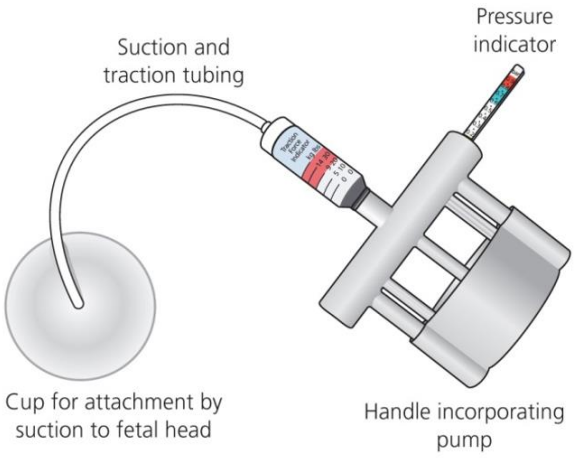

Figure 12: *A diagram of the ventouse from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

The use of these devices is not without the risk of complications, both methods can fail, in particular the ventouse if the cap is not correctly placed. The suction of the cap can also cause a swelling on the fetal head known as a 'chignon' which will decrease over a matter of hours. More serious complications include fetal scalp lacerations, facial nerve damage and skull fractures in the fetus as well as third degree tears and postpartum haemorrhage in the mother (82).

Instrumental deliveries can be used to assist the vaginal delivery of twins, particularly in the second twin if there is difficulty delivering the fetal head after vaginal breech extraction manoeuvres or if there is fetal distress and delivery needs to be expedited.

1.5.3.4 Caesarean section

Caesarean sections can be indicated for a variety of reasons. Women who have a placenta covering the cervix – placenta praevia will require this method of delivery and those with antenatal complications such as gestational diabetes or pre-eclampsia may be advised that a caesarean section is safer than vaginal delivery (81). In other cases it will be used for emergencies, such as placental abruption where the placenta detaches from the uterus before delivery of the fetus(es), or fetal distress during labour (81, 83).

The operation is usually performed under spinal anaesthesia however it can be carried out using epidural anaesthesia in emergency cases or general anaesthetic in critical cases. The fetus(es) are delivered via a suprapubic transverse incision through the layers of the abdominal wall and uterus (figure 13), which can be carried out in a matter of minutes if necessary (82, 84).

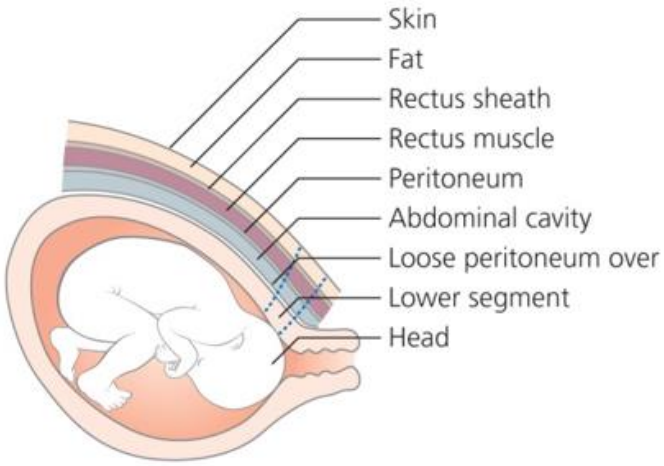

Figure 13: *A diagram of the layers of the abdominal wall through which an incision is made in a caesarean section from Obstetrics and Gynaecology, 5th Edition by Lawrence Impey & Tim Child – permissions granted by John Wiley & Sons, Inc.*

Despite caesarean section being the safest delivery option in a lot of cases there are risks involved. For the mother there is risk of damage to internal organs such as the bladder and bowel,

haemorrhage and the need for blood transfusion and due to post-operative immobility there is a risk of venous thromboembolism – blood clots in the legs and lungs (82, 84). A caesarean section is major abdominal surgery which will take time to recover from therefore mobility after the surgery and caring for the new-born is often more difficult and will require assistance. For the fetus there is a risk of lacerations and respiratory morbidity due to the fluid in the lungs not being expelled as the fetus passes through the birth canal (82).

1.6 Delivery in twins

The labour and delivery of a twin pregnancy is likely to be more complicated than in singletons, particularly as multiple pregnancies are more likely to face complications and adverse outcomes from intrapartum events (85). There are various aspects that can prove challenging such as the intrapartum monitoring of both fetuses, the delivery of the second twin, the need for instrumental and operative interventions and the optimum inter-twin delivery interval.

1.6.1 Monitoring twins during labour

Due to the complex nature of multiple pregnancies it is vital that the fetuses are continuously monitored throughout labour so that any indications of fetal distress of one or both fetuses can be detected early and immediately acted upon. The use of continuous monitoring of FHR by CTG in twins is recommended by NICE (49) due to the inability of manual methods to detect both fetal heart rates. However, using CTG monitoring in twin pregnancies can be challenging, particularly in ensuring that both twins are be being accurately assessed. For this to be the case, there must be separate and good quality CTG traces for each twin, making sure that the traces produced are not from the same fetus can be difficult. During labour the use of a fetal scalp electrode on the leading twin can improve monitoring (86).

The interventions to resolve fetal distress or expedite delivery in twins may be more complicated and require the skill of experienced obstetricians demonstrating the need for close monitoring and low threshold for suspicion of complications.

1.6.2 Vaginal delivery of twins

Vaginal delivery is often an option for most multiple pregnancies. There are various circumstances in which this mode of delivery is not advised including triplets and higher order multiples, MCMA twins, non-cephalic leading twin and certain maternal and fetal antenatal complications (81).
Many women pregnant with twins who opt for a vaginal delivery have an induction of labour to optimise the timing of the delivery. This is to balance the increasing risk of stillbirth with gestational age and effects of prematurity if delivered too early. NICE recommends delivery of DCDA twins from 37^{+0} weeks gestation, MCDA twins from 36^{+0} weeks and MCMA twins between 32^{+0} and 33^{+0} (49). For the delivery of MCDA and MCMA twins NICE also recommends considering a course of antenatal corticosteroids (49). The use of corticosteroids is to promote pulmonary maturity in fetuses delivered before term, thereby reducing perinatal morbidity and mortality (87).
Labour can be induced by various methods and the success of this depends on the favourability of the cervix. Before any methods are used an assessment of the cervix is made which looks at various factors; consistency of the cervix, degree of effacement, station of the head, position of the cervix in the pelvis and cervical dilation. Each of these will score various points known as the Bishop's score and suggest the likely success of induction and progression to vaginal delivery, a score of more than six is favourable and less than five is unfavourable and suggests the need for cervical ripening (75, 88). There are several methods for induction of labour, if cervical ripening is needed prostaglandin E_2 can be administered vaginally or this can be achieved with the use of a transcervical balloon catheter. If cervical ripening is not required the membranes can be artificially ruptured and oxytocin administered to encourage uterine contractions (88).

1.6.3 Pain relief in twin delivery

NICE advises discussing pain relief options with women pregnant with twins who are planning a vaginal delivery. They recommend the use of epidural anaesthesia and state this should increase the chance of a successful vaginal delivery of all babies and allow for a faster emergency caesarean section if this is required (49).

1.6.4 Delivery of the second twin

For twin pregnancies that go on to deliver vaginally the principles and mechanism of labour for the leading twin are much the same as for singletons. The difficulties that are faced in twin vaginal delivery tend to arise with the delivery of the second twin, which may not be in a presentation compatible with vaginal delivery. If this is the case after the delivery of the leading twin, then external cephalic version (ECV) can be performed. In this procedure the fetus is rotated into a longitudinal lie by applying manual pressure to the abdomen, this is usually performed under ultrasound (89). If this is unsuccessful and the transverse or oblique lie of the fetus persists, another manoeuvre known as internal podalic version can be trialled. Where possible this is carried out in theatre in case of emergency, and adequate analgesia, ideally regional anaesthesia, should be used. During the manoeuvre the obstetrician's hand reaches into the vagina and fully dilated cervix to grasp one of the fetus' heels, they then pull the heel down into the mother's pelvis which will cause the fetus to rotate, at this point an episiotomy can be considered, this is a cut made in the perineum to create more space for the fetus to be delivered, the arms and shoulders are then carefully delivered followed by the rest of the body (76, 90).

Another issue that can be faced is loss of contractions between the delivery of the leading and second twin. This is common and the contractions will usually restart within a few minutes however

if this does not occur, oxytocin can be used to encourage uterine activity. In this period between the delivery of each twin it is important to closely monitor the second twin for signs of fetal distress via CTG as there is increased risk of intrapartum hypoxia (54). NICE recommend that the delivery interval between each twin should be a maximum of 20 minutes, with other guidelines advising up to 30 minutes (49, 91). A longer interval can lead to increased morbidity for the second twin (54). Emergency caesarean section to deliver the second twin is not uncommon, occurring in 10-15% of cases and should be discussed when counselling patients on delivery method. This can happen in cases of persistent malposition, umbilical cord prolapse, failure to progress and fetal distress (92).

1.6.5 Caesarean delivery in twins

As previously mentioned, in some twin pregnancies vaginal delivery is absolutely contraindicated, this is the case for conjoined and MCMA twins. In other situations, caesarean delivery is indicated and these include non-cephalic leading twin and any maternal or fetal condition likely to worsen during labour or complicate the delivery e.g. pre-eclampsia, diabetes mellitus and placenta accreta/ praevia (82, 85). In some multiple pregnancy cases the mothers will elect to have a caesarean section by their own choice or end up with an emergency caesarean section if attempt at vaginal delivery is unsuccessful or there is fetal compromise.

1.7 Conclusion

Current guidance and existing literature highlight the challenges that are faced in the antenatal and intrapartum management of multiple pregnancy. Compared to singletons, multiple gestations require more extensive surveillance throughout pregnancy, particularly in MC pregnancies, due to the greater risk of complications due to shared placentation and pre-term birth. The delivery of

twins is complex with many aspects to balance, including timing, mode and fetal monitoring. In a world where the multiple pregnancy rate is increasing it is necessary to ensure that there is adequate evidence-based guidance to support clinicians in managing these high-risk pregnancies.

Chapter 2: A comparison of International guidelines on the management of multiple pregnancy

2.1 Introduction

The provision of safe and effective care to a woman and her fetuses throughout a pregnancy is vital to ensuring a safe delivery and good outcomes for both the mother and her babies. Over the course of a twin pregnancy, women will interact with multiple health professionals at a range of different appointments. At these they will be offered various tests that will help determine the risk of the pregnancy, the level of surveillance they will need and any interventions they might need. The guidance that is followed will help to develop a management plan that will ensure adequate monitoring of the mother and fetuses.

2.1.1 UK-based antenatal management

In standard UK practice at the start of pregnancy the woman will meet with a healthcare professional to discuss her medical history, family medical history and lifestyle to identify any potential maternal and fetal risks. They will then be referred for routine tests including tests to identify blood group, Rhesus factor and any serious infections with potential consequences for the fetus, such as rubella, syphilis and HIV (93). Towards the end of the first trimester women are offered an ultrasound scan to determine the gestational age of the fetuses as well as aneuploidy screening tests to determine the risk of genetic conditions such as Down's Syndrome and Edward's syndrome (93). At this scan it is also possible to identify whether there are separate placentas supporting the fetuses or a fused placenta – this is known as chorionicity and will influence the routine management of the pregnancy. When the fetuses each have a separate placenta – known as dichorionic (DC), there is generally less risk involved and hence less surveillance required. However, if there is a fused placenta supporting both fetuses – monochorionic (MC), there is a greater level of risk involved. This is due to a single blood supply being shared between the two fetuses; this can

lead to imbalances in the volume of blood that each twin receives. This situation, when it arises is has a high level of risk of morbidity and mortality for both fetuses (94) and so it is vital that MC twins are monitored more frequently and in greater depth. All women are offered another scan between 18^{+0}-20^{+6} weeks, described as an 'Anomaly' or 'Anatomy' scan which takes a more in depth look at the fetuses and their organs to check for any complications that pose risk to the fetus either during pregnancy or shortly after birth. This scan is carried out in accordance with the NHS Fetal Anomaly Screening Programme (FASP) standards. There are a number of specific images that need to be obtained to complete the screening including images of the brain, heart and spine, if these are unable to be taken at the first scan, another one should be arranged before 23^{+0} weeks (95). Conditions that may be detected at this appointment include cleft lip, spina bifida and congenital heart disease (96).

2.1.1.1 Dichorionic twin pregnancy

As mentioned, if the pregnancy is DC with the fetuses each receiving their own blood supply then the risk of fetal complications throughout the pregnancy is lower in comparison to MC twins (97). The level of monitoring for DC twins, is more rigorous than in a singleton pregnancy. The UK National Institute for Health and Care Excellence (NICE) provides guidance on the antenatal management of a dichorionic pregnancy, they recommend ultrasound appointments to measure the growth of the fetuses and screen for any complications every four weeks from twenty weeks gestation. Figure 14 outlines the schedule of antenatal appointments for a DC twin pregnancy according to NICE 2019 (49).

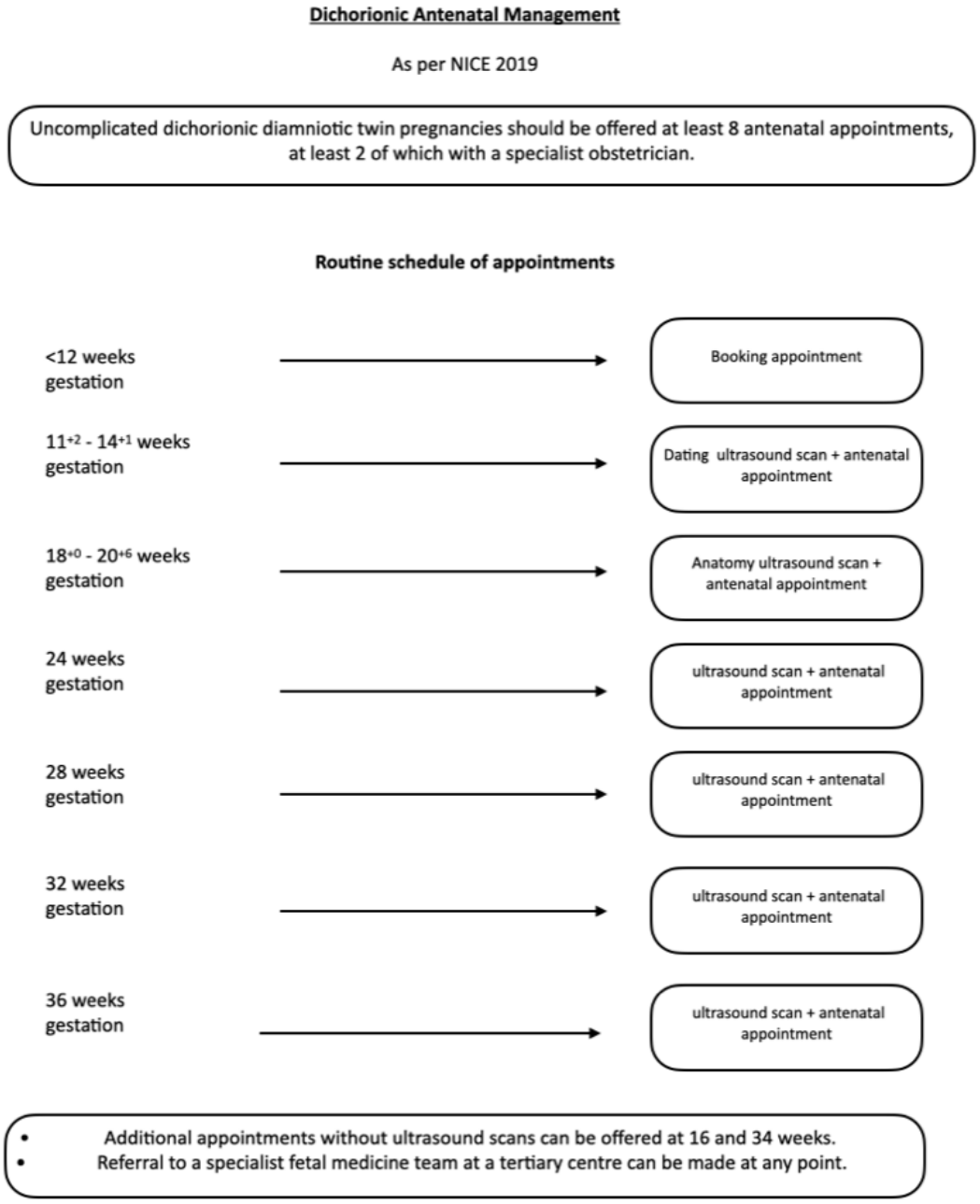

Figure 14: *A diagram of the antenatal appointments in a dichorionic twin pregnancy*

2.1.1.2 Monochorionic twin pregnancy

MC twin pregnancies in which the fetuses share a placenta and blood supply are at increased risk of complications, more so than in DC twins (98, 99). There are conditions that can arise due to imbalances in blood flow known as Twin to Twin Transfusion Syndrome (TTTS) and Twin Anaemia

Polycythemia Sequence (TAPS). These conditions, particularly when severe, can have serious implications for both twins (70, 100, 101) and so it is vital that they are recognised as early as possible. To detect TTTS and TAPS, various measurements of arterial blood flow and the volume of amniotic fluid surrounding the fetuses are taken by ultrasound, these include doppler assessment of umbilical artery flow, middle cerebral artery-peak systolic velocity (MCA-PSV), fetal bladder volumes and maximal vertical pocket (MVP) of amniotic fluid (19, 49, 91, 102). For MC twins NICE recommends ultrasound appointments every two weeks (49) (figure 15). Screening for TTTS and TAPS should take place from sixteen weeks gestation by measuring MVP, MCA-PSV and doppler assessment of umbilical artery flow (49). MC twins are also at increased risk of sFGR, therefore from sixteen weeks gestation they should also be monitored for fetal weight discordance using two or more biometric parameters, for example abdominal circumference, head circumference or femur diaphysis length. Estimated fetal weight discordance (EFW) should be measured and recorded with increased monitoring for cases where EFW discordance is 20% or above and referral to a tertiary centre if 25% or above (49).

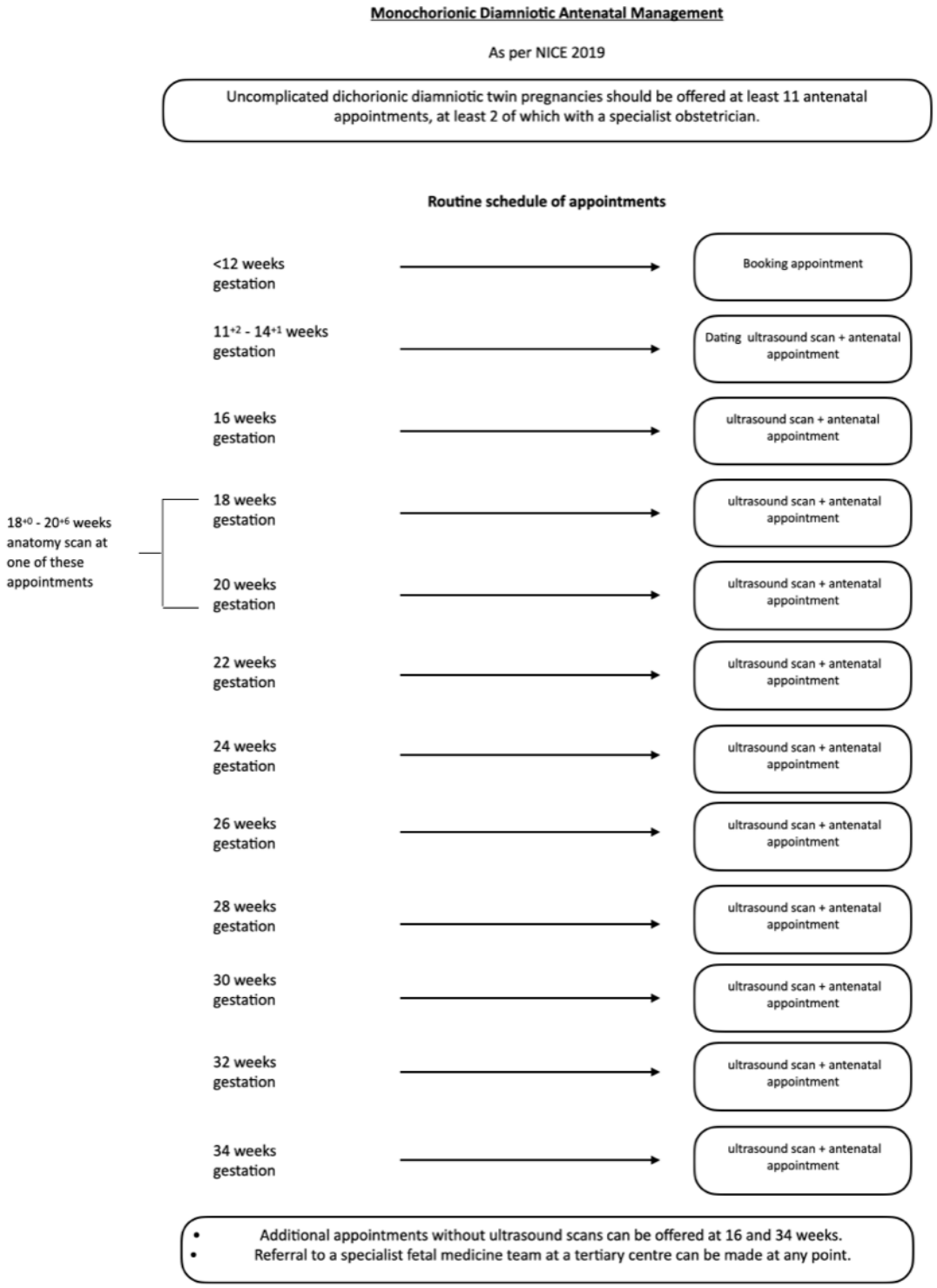

Figure 15: *A diagram of the antenatal appointments in a monochorionic twin pregnancy*

2.1.1.3 Monoamniotic twin pregnancy

MCMA twins where the fetuses share an amniotic sac can also be affected by TAPS, FGR and have a perinatal mortality rate between 30%-40% (69). Cord entanglement, one of the classic features of an MCMA pregnancy is at risk of progressing to cord compression which threatens the blood supply to the fetuses. Because of these complications and the risks involved in an MCMA twin pregnancy, NICE guidance recommends referring these cases to specialist centre to receive individualised care (49).

2.1.2 Intrapartum management

The birth of twins may be more complicated than for singletons. There are various extra factors that have to be considered; the position of the fetuses, how to monitor both fetuses throughout labour and the optimum time between delivery of the leading and second twin. All of these aspects make the management of labour more complex therefore requiring the involvement of specialist clinicians in a centre capable of managing complex births.

One of the major areas for debate in the delivery of twins is the optimum timing of birth, with various factors to be considered this is a careful balancing act. Where possible the time spent in utero should be maximised, allowing the fetuses to continue to develop and increase lung maturity. However, with increasing gestational age the risk of still birth also increases, but if delivered too early the morbidity associated with prematurity can be extensive (103). There are also various circumstances which are associated with increased risk of intrauterine death and perinatal mortality such as the cord entanglement observed in MA twins which is at risk of cord compression, potentially leading to the death of one or both of the fetuses without warning (70, 104).

The risks involved with twin pregnancies, particularly MA twins mean that most twins are delivered by caesarean section (105). However UK NICE guidance states that in DCDA or MCDA twins a vaginal

delivery is safe providing the pregnancy is uncomplicated and past 32 weeks gestation, the leading twin is cephalic and there are no contraindications to labour (49).

2.1.3 The need to review current guidance

As highlighted, twin pregnancies are not straight forward. From the moment of identifying that there are two fetuses present within the uterus there are many risks to navigate; screening and/or diagnostic testing, management of monochorionic complications, growth surveillance with detailed planning throughout. There are many vital timepoints at which surveillance or intervention is needed to optimise fetal outcomes. To enable clinicians to run services and deliver care capable of achieving this there must be detailed, evidence-based guidelines that are easily followed and implemented. The aim of this chapter is to review current international guidelines, highlighting areas of consensus and conflict and identification of aspects which require further evidence.

2.2 Methods

2.2.1 Search strategy

Before starting the search for guidelines, criteria for inclusion and exclusion were developed. It was decided to exclude guidelines produced prior to 2010, this is due to developments in the understanding of monochorionic pregnancy complications and screening techniques. We included guidelines in multiple languages provided that we were able to translate these. Guidance from countries of all levels of economic development were included.

The search started in September of 2021 starting with a search of the online health databases Medline, Pubmed, Scopus, Academic Search Complete, CINAHL as well as ERCI Guidelines website.

The search terms throughout the search process were ‘multiple, pregnancy’, ‘twin, pregnancy’ or ‘multiple, gestation’. Where possible, results were limited to ‘practice guidelines’ in terms of article type and the following MESH terms were applied: ‘pregnancy, multiple’, ‘pregnancy, twin’, ‘prenatal care’, ‘obstetrics’, ‘delivery, obstetrics’, ‘pregnancy complications’, ‘pregnancy outcome’ and ‘practice guideline as topic’. The results were then screened for relevance and eligibility with nine guidelines included. A PRISMA diagram of the initial search is included (Figure 16).

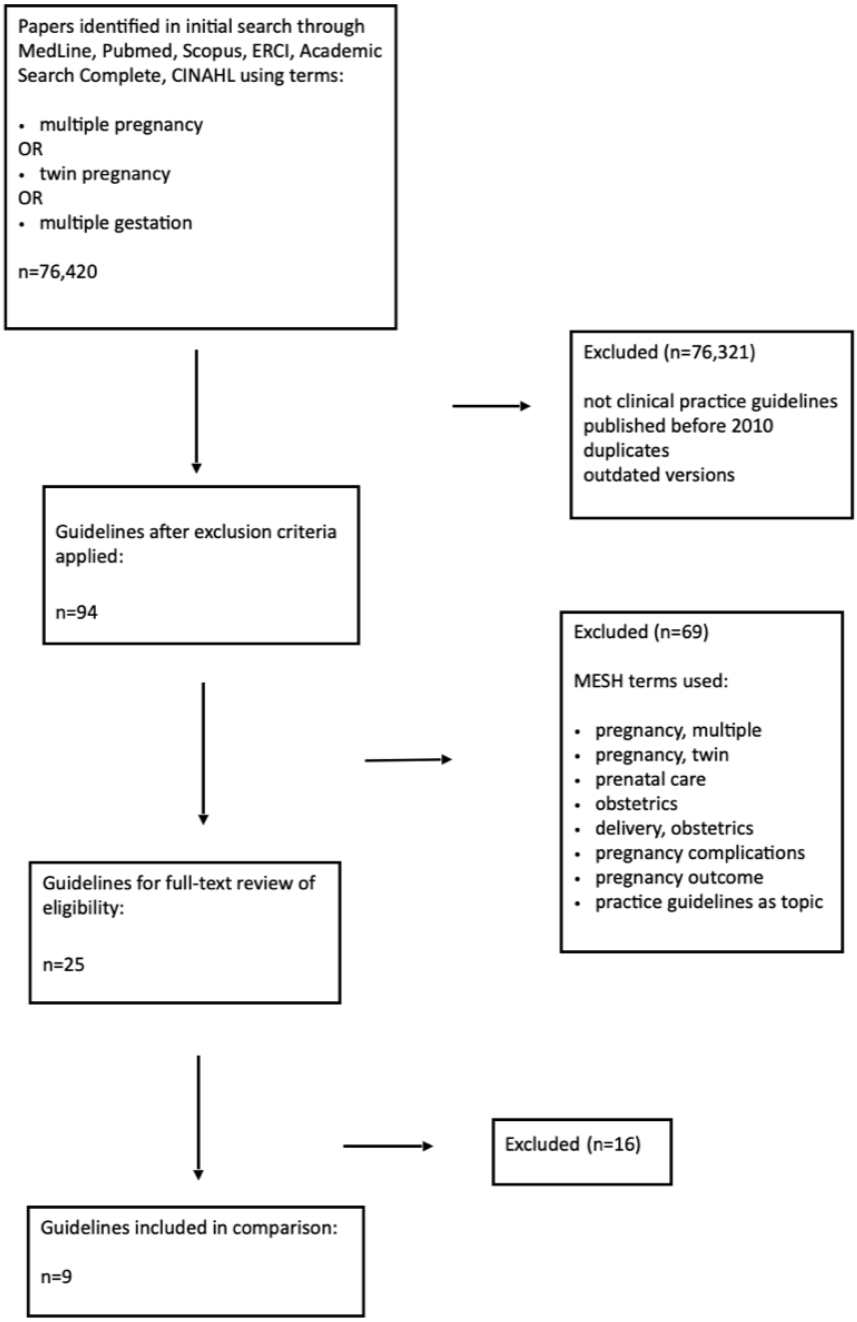

Figure 16: *A PRISMA diagram summarizing the initial database search*

From the initial search it was evident that some of the major societies who have produced guidelines were not identified by these searches. It was then decided to do a further hand search of the websites of professional societies and an internet search of countries we expected to have produced guidelines.

It was also noted that some professional bodies may have guidance on the management of multiple pregnancy within other guidelines rather than as a separate document, so from this another search was conducted through the databases Medline, Pubmed, Scopus and Academic Search Complete as well as websites Guideline Central, Up to Date and ERCI Guidelines. The terms 'labour' or 'intrapartum' and 'guidelines' were used and the same exclusion criteria was applied. Again, where possible the MESH terms 'delivery, obstetric', 'obstetrics' 'fetal monitoring', 'labour, obstetrics', 'labour, induced', 'breech presentation', 'vaginal birth after c-section', 'gestational age', 'pregnancy complications' and 'fetal membranes' were used and results were screened for relevance and eligibility. We identified one further guideline, totalling twenty-one guidelines. A PRISMA diagram for this additional search is also displayed (figure 17).

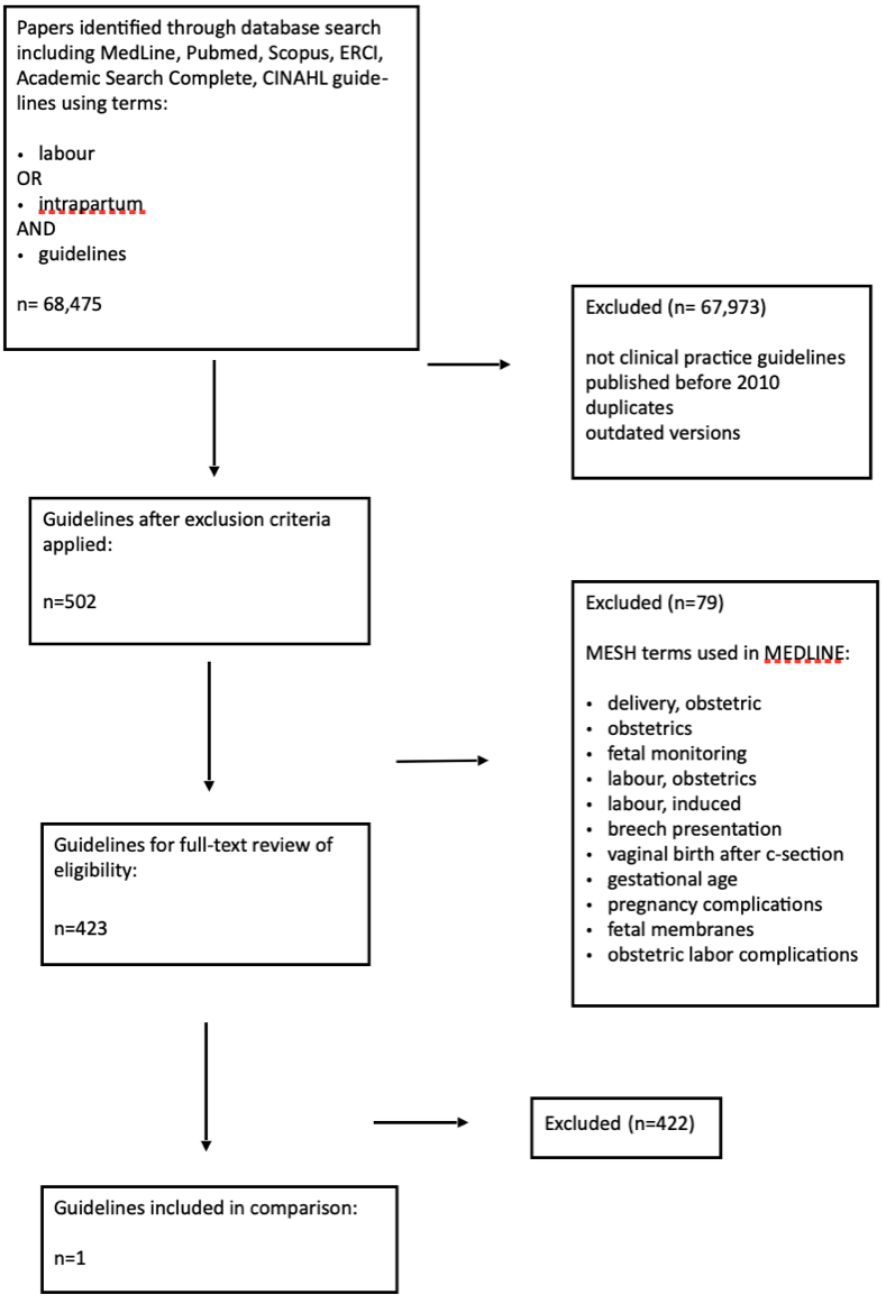

Figure 17: *A PRISMA diagram summarizing the further database search*

There were three guidelines which were not published in the English language, these were translated by native speakers with a clinical background to assess the eligibility and extract relevant data.

2.2.2 Summarising information

A standard data extraction tool (figure 18 and 19) was developed and used to obtain information on key points; antenatal screening and timing of ultrasounds, assessments for TTTS, cervical length and pre-term birth prevention, the timing and mode of birth and intrapartum care. The guidelines that were deemed to be eligible were read and relevant information was collected.

Country	Guideline organisation & Year	Types of multiple pregnancy included	Dating scan & timing (weeks)	Determination & timing of chorionicity & amnionicity (weeks)	Placenta placement	Twin labelling & method	Fetal Anomaly Scan timing (weeks)	Screening for Aneuploidy	Ultrasound frequency for DCDA (weeks)

Ultrasound frequency for MCDA (weeks)	Ultrasound frequency for MCMA (weeks)	Ultrasound frequency for complex (weeks)	Screening for TTTS:	Screening for TTTS: Umbilical artery flow assessment?	Screening for TTTS: MCA-PSV measurement?	Fetal growth measurem-ents	Fetal echocardio-gram	Cervical Length assessment	Preterm birth prevention	Administration of Corticosteroids

Figure 18: *The antenatal data extraction tool used to collate information from the international guidelines (DCDA: dichorionic diamniotic, MCDA: monochorionic monoamniotic, MCMA: monchorionic monoamniotic, TTTS: twin to twin transfusion syndrome, MCA-PSV: middle cerebral artery – peak systolic velocity)*

Country	Guideline organisation & Year	Types of multiple pregnancy included	Timing of Birth (weeks): DCDA	Timing of Birth (weeks): MCDA	Timing of Birth (weeks): MCMA	Timing of Birth (weeks): Complications	Mode of birth: DCDA

Mode of birth: MCMA	Mode of birth: 2nd twin non cephalic	Intrapartum fetal monitoring	Analgesia	Delivery interval	Intrapartum care	Management of 3rd stage of labour

***Figure 19**: The intrapartum data extraction tool used to collate information from the international guidelines*

***(**DCDA: dichorionic diamniotic, MCDA: monochorionic monoamniotic, MCMA: monchorionic monoamniotic)*

2.3 Results

2.3.1 Description of sources

The search produced twenty-one national guidelines from sixteen countries as well as two international guidelines. These had been produced by the Australia and New Zealand (RANZCOG), Canada (JOGC), Denmark (DSOG), France (CNGOF), Germany (AWMF), Ireland (IOGRCPI), Italy (SIGO), Japan (JAOG), Mexico, Netherlands (NVOG), North America (ACR, SMFM, ACOG, NAFTnet), Oman (Oman MOH), Poland (PGS), Sri Lanka (SICOG), UK (NICE and RCOG). The international

guidelines were from The international Society of Ultrasound in Obstetrics (ISUOG) and The International Federation of Gynaecology and Obstetrics (FIGO).

2.3.2 Results tables

The tables 1 and 2 display the results from the data collected from the guidelines.

Table 1: *A table displaying the antenatal results from comparison of international guidelines on the management of multiple pregnancy. (DCDA: dichorionic diamniotic, DC: dichorionic, MC: monochorionic, MCDA: monochorionic monoamniotic, MCMA: monchorionic monoamniotic, TTTS: twin to twin transfusion syndrome, MCA-PSV: middle cerebral artery – peak systolic velocity, CL: cervical legnth)*

Aspect of Care	Result
Determination of Chorionicity and Amnionicity	• Within first trimester: 100% agreement
Twin labelling	• Recommended by 42.9% (9/21)
Anomaly Scan	• Recommended by 57.1% (12/21) *Timing* • 18-22 weeks gestation: 11/12 • 20-22 weeks gestation 1/12
Frequency of Ultrasound in DC twins	• Every 2 weeks: 9.5% • Every 4 weeks: 47.6% • Every 5 weeks: 4.8% • Every 4-6 weeks: 4.8%

	• No guidance: 33.3%
Frequency of Ultrasound in MCDA twins	• Every 1-2 weeks: 4.8% • Every 2 weeks: 57.1% • Every 2-3 weeks 19.0% • Every 2-4 weeks 4.8% • No guidance: 14.3%
Frequency of Ultrasound in MCMA Twins	• Every 1-2 weeks: 4.8% • Every 2 weeks: 33.3% • Every 2-3 weeks: 14.3% • Every 2-4 weeks: 4.8% • No guidance: 38.1%
Screening for TTTS	• Recommended by 90.0% *Measurements* • Amniotic fluid volumes: 47.6% • Amniotic fluid volumes & visualise bladders: 38.1% • Not mentioned: 14.3%
Umbilical Artery flow	· Recommended by 52.3% *Indication* • At every ultrasound: 23.8% • If discordances in growth or fluid volumes: 14.3% • If TTTS suspected 4.8% • After 16 weeks: 4.8% • After 20 weeks: 9.5%

	• No guidance: 28.6%
MCA-PSV measurement *(specific to MCDA twins)*	· Recommended by 52.3% *Indication* • At every ultrasound: 14.3% • After 20 weeks gestations: 23.8% • If abnormal umbilical artery doppler without explanation: 4.8% • Recommended but unclear on timing: 14.3% • No guidance: 42.9%
Fetal growth measurements	• Recommended by 85.7%
Fetal echocardiogram *(specific to MCDA twins)*	*Indication* • On an individual basis: 4.8% • In MC twins: 14.3% • At 18-22 weeks gestation: 9.5% • No guidance: 66.7%
Cervical length assessment	*Recommended* • Yes: 33.3% • No: 23.8% • Undecided: 9.5% • Not mentioned: 33.3%
Pre-term birth prevention	*Recommendations* • No interventions: 42.9%

	• Vaginal progesterone in individual cases: 4.8% • Cervical pessary (CL <25th centile): 4.8% • Not mentioned: 47.6%

Table 2: *A table displaying the intrapartum results from comparison of international guidelines on the management of multiple pregnancy DCDA: dichorionic diamniotic, DC: dichorionic, MC: monochorionic, MCDA: monochorionic monoamniotic, MCMA: monchorionic monoamniotic, VBE: vaginal breech extraction)*

Aspect of Care	Result
Timing of birth in DCDA twins	• 36 weeks: 4.8% • 37 weeks: 4.8% • 37^{+0} – 38 $^{+0}$ weeks: 9.5% • 38^{+0} – 38 $^{+6}$ weeks: 4.8% • 38– 40 weeks: 4.8% • 38 $^{+0}$ weeks: 9.5% • Before 40 weeks: 4.8% • Not mentioned in guidelines covering DCDA twins: 38.1%
Timing of birth in MCDA twins	• 34^{+0} – 37^{+6} weeks: 9.5% • 36 weeks: 14.3% • 36^{+0} – 37 $^{+0}$ weeks: 19.0% • By 37 weeks: 9.5% • 36- 38 $^{+6}$ weeks: 4.8% • Not mentioned in guidelines covering MCDA twins: 38.1%

Timing of Birth in MCMA twins	• 32^{+0} – 33^{+0} weeks: 9.5% • 32^{+0} – 34^{+0} weeks: 38.1% • By 34 weeks: 4.8% • 33-36 weeks: 4.8% • Not mentioned in guidelines covering MCMA twins: 38.1%
Mode of birth in DCDA twins	• Vaginal if leading twin is cephalic: 38.1% • Vaginal if both twins are cephalic: 4.8% • Vaginal delivery considered: 14.3% • Elective caesarean section: 4.8% • Not mentioned: 38.1%
Mode of Birth in MCDA twins	• Vaginal if leading twin is cephalic: 28.6% • Vaginal if both twins are cephalic: 4.8% • Vaginal delivery considered: 28.6% • Elective caesarean section: 4.8% • Not mentioned: 33.3%
Mode of birth in MCMA twins	• Elective caesarean section: 71.4% • Not mentioned: 28.6%
Mode of birth is second twin is non-cephalic	• VBE & manoeuvres to turn baby considered: 23.8% • VBE: 9.5% • Not mentioned: 70.0%
Intrapartum fetal monitoring	• Use of CTG: 33.3% • Use of fetal scalp electrode: 9.5% • Not mentioned: 70.0%

Analgesia	• Epidural anaesthesia recommended: 23.8% • Not mentioned: 76.2%
Intertwin delivery interval	• 20 minutes: 4.8% • Within 30 minutes: 14.3% • Longer than 30 minutes with appropriate monitoring: 4.8% • Not mentioned: 76.2%
Management of 3rd stage of labour	• Active management: 19.0% • Not mentioned: 81.0%

2.3.3 Unanimous recommendations and those with a high level of agreement

The determination of amnionicity and chorionicity within the first trimester was recommended by all sources. In those that recommended a fetal anomaly scan, 91.6% advised that this should take place between 18-22 weeks. 90.0% encouraged screening for TTTS and 85.7% recommended serial fetal growth measurements. In those that provided advice in these areas, all advised caesarean section to deliver MCMA twins, epidural anaesthesia for intrapartum analgesia and active management of the third stage of labour.

2.3.4 Conflicting recommendations

The frequency at which to monitor twin pregnancy by ultrasound causes some conflict. In DCDA twins the time between surveillance varies between every 2 weeks (recommended by 9.5%), to 4-6 weeks which was suggested by one guideline with every 4 weeks recommended by 47.6%.

In MCDA twins the range is between every 1-4 weeks with every 2 weeks recommended by 57.1%. This is similar for MCMA twins with the same range but 33.3% advising every 2 weeks and 14.3% recommending every 2-3 weeks.

52.3% advised assessing umbilical artery flow but the indication under which this is done varies. The indications include if TTTS is suspected, if there are discordances in growth or fluid volumes or at every ultrasound which is advised by 23.8%.

There is similar conflict in the measurement of MCA-PSV, a doppler measurement primarily used in the assessment of MCDA twins. 52.3% recommend assessing with the indications for doing so varying. Of those that gave advice, most advised after 20 weeks gestation (23.8%) with others recommending only if there is an abnormal UAPI without explanation.

One of the main inconsistencies in advice is the assessment of cervical length as a predictor for preterm birth. 33.3% recommend measuring cervical length, 23.8% advise against doing so with the remaining 42.8% either undecided or not mentioning this within their guidance. 42.9% of institutions advise no interventions for preventing pre-term birth with only two institutions recommending either vaginal progesterone or cervical pessary in individual cases.

The optimum timing of delivery caused some degree of conflict in all types of twins. For DCDA twins the range is between 37 and 40 weeks with a maximum of two guidelines agreeing a particular time (37^{+0} - 38^{+0} weeks and 38^{+0} weeks). In MCDA twins the range is greater, from 34+0 weeks to 38+6 weeks (only one guideline advising the latter). However, 19.0% agree on advising delivery between 36^{+0} and 37^{+0} weeks. There is less discrepancy in MCMA twins but no majority opinion is reached.

38.1% recommend birth between 32^{+0} and 34^{+0} weeks gestation with only one guideline advising up to 36 weeks gestation.

For DCDA twins, vaginal delivery is suggested by 57.2% however there are conditions surrounding these recommendations. 38.1% will advocate vaginal delivery if the leading twin is cephalic and one guideline advises only if both twins are cephalic. The situation is similar with MCDA twins, 28.6% advise vaginal delivery if the leading twin is cephalic, 28.6% state it is considered and one guideline (4.8%) recommending only if both twins are cephalic.

Intrapartum care including intrapartum fetal monitoring, analgesia, mode of birth if the second twin is non-cephalic and intertwin delivery interval lacks guidance. 52.4% of guidelines did not provide any advice for this aspect of management of multiple pregnancy.

2.4 Discussion

2.4.1 Demographics

All except two of the guidelines were from more economically developed countries (MEDCs). Organisations within these countries make up a large proportion funding for health research that will impact these guidelines (106). In addition, these countries have the resources and infrastructure to practice evidence-based medicine and deliver high quality care with the latest technologies. This provides them with a sound platform from which to conduct research and develop guidelines that less economically developed countries are less likely to have. Despite not allowing an exploration of the care that is given and how this is delivered in LEDCs, the guidelines identified reflect the populations that will be explored throughout this project and are therefore more relevant.

2.4.2 Pre-term birth

No societies recommend an intervention for prevention of pre-term birth. This is reflected by the current lack of evidence to highlight any one intervention that is able to effectively prevent pre-term birth and improve perinatal and neonatal outcomes in multiple pregnancy. *Jarde et al* conducted a systematic review and meta-analysis of randomised controlled trials where progesterone, cerclage or pessary were used as a preterm birth prevention in asymptomatic twin pregnancies. Included were 23 trials looking at over 6500 women pregnant with twins, concluding that there was no significant reduction in risk of preterm birth between 34 to 37 weeks gestation by any of the interventions compared to the control. However, it was found that vaginal progesterone reduced the risk of requiring ventilation and early neonatal death in some cases (107). A recent systematic review and meta-analysis by the EPPPIC Group however evaluated the use of progesterones as a prevention for pre-term birth and found that in twins and higher order pregnancies, there was no benefit (108). Interestingly, a third of the same societies promote cervical length screening to predict pre-term labour without offering any interventions if the woman does go into preterm labour. There is a fine balance between effectively utilising available technology and offering numerous tests without the guidance to act upon the findings. The rationale of screening for cervical length raises questions about this balance.

2.4.3 Dichorionic Twin Pregnancies

Almost 20% of societies didn't provide guidance for DC twins and concentrated solely on MC twins. Undoubtably MC twins have much higher rates of complications and require more frequent and in-depth surveillance (97, 98, 109). Therefore, clear guidance is necessary to ensure these pregnancies are managed appropriately and have the best outcomes possible. However, that does not mean to

say that DC twins are a simple, straightforward pregnancy. As previously discussed all multiple pregnancies are by nature more complicated (21) and often present complex clinical challenges. They should therefore, involve a detailed management plan involving a multidisciplinary team, so the question is raised as to why these societies fail to produce guidance for these twins and highlights the importance for comprehensive, unified guidance.

This need is further exemplified by the conflict on when to start ultrasound surveillance in DC twins and the frequency at which this should take place. The advice ranges from every 2 weeks to every 5 weeks with most societies somewhere in between. This variation in guidance is confusing and questions the evidence each society is using to justify their intervals. In a multicentre prospective cohort study 789 dichorionic twin pregnancies underwent sonographic surveillance for fetal growth restriction (FGR) every 2 weeks. Data from this was then compared to simulated data where the ultrasound assessment was every 4 weeks and found that the detection of FGR decreased from 88% to 69% and detection of an abnormal umbilical artery doppler reduced from 82% to 62% with the longer interval in assessment (110). However, due to the data being simulated these findings may not truly reflect clinical practice but they do highlight the risk of failing to detect or delayed detection of complications when the time between surveillance is increased. Clearly, more evidence is required to identify the optimal timing and frequency of surveillance to increase the chance of detecting complications whilst ensuring positive patient experience is preserved.

Another area of divided opinion is the timing and mode of birth in DC twins. The results show that only two sets of guidance out of twenty agreed on an optimum timing of birth in these twins with suggested times ranging from 37^{+0}-40^{+0} weeks gestation. This lack of consensus is confusing and mirrors the current literature where there is a range of data suggesting conflicting preferred timings for the delivery of DCDA and MCDA twins (38, 103, 111, 112). Optimum timing of delivery is a difficult balance of preventing the complications of prematurity versus risk of still birth with increasing gestational age and is often individualised in many cases. However, the conflict in

guidance does not aid this or provide reassurance. Over half of the guidelines mentioned vaginal delivery as an option for the mode of birth in DCDA twins but the conditions on when this is recommended varies. The majority allow vaginal delivery if the leading twin is cephalic, Japan advises only if both twins are cephalic and 14.3% state it can be 'considered'. The language used is important, phrases such as 'aim for' or 'can be considered' give a sense of hesitation or lack of confidence in the option of vaginal delivery for twins. For a delivery which will often be more complex than a singleton vaginal delivery guidance around this should be decisive and supportive with the conditions around when this mode of delivery should be encouraged being clear and unified. Again, the need for evidence based, well defined guidance from all institutions is exemplified.

2.4.4 Monochorionic Twin Pregnancies

From the guidance we found the management of MC twin pregnancies was generally well covered and considerably detailed due to the risks and outcomes involved in these pregnancies. As in DC twins there were discrepancies in the frequency of ultrasound scans and timing of birth but these had a higher level of agreement and less variation than in DC twins. Looking at the mode of delivery there is complete agreement that MCMA twins should be delivered via caesarean section due to the risk of acute cord entanglement and locked twins (70, 113). However, in MCDA twins there was less agreement and the language used was again similar to the picture seen in DC twins. In the guidance for MCDA twins there was with greater emphasis on allowing vaginal delivery if not contraindicated but clarification on which conditions and circumstances are classed as a contraindication was brief if included.

The indication and rationale for when to assess the UAPI and MCA-PSV was mixed. These measurements, taken via ultrasound help to determine whether the pregnancy is affected and how

severely, by placental insufficiency or imbalances such as TTTS or TAPS. These conditions have adverse fetal and neonatal outcomes if not detected and treated appropriately (24, 55, 58, 101). Therefore, it is vital that a clear strategy of surveillance is followed, and this is not reflected in the guidance. Suggested indications include if TTTS is suspected, if there is discordance in growth or fluid volumes. Almost 25% recommend taking umbilical artery Doppler measurements at every ultrasound, 14% for MCA-PSV, with a few stating only after 16 or 20 weeks. In MC twin pregnancies the threshold for suspecting TTTS or similar placental disorders is generally low given the nature of the condition, however it should be questioned whether those suggesting only to take measurements after 20 weeks or if other ultrasound findings indicate to do so will miss or delay detection. The onset of TTTS is usually in the second trimester, however a case-series and systematic review looked at 215 cases of early-onset TTTS with a diagnosis <18 weeks gestation. It was found that these cases had worse fetal and neonatal outcomes than those seen in later onset TTTS and despite these cases representing a small proportion of TTTS cases they make up a large proportion of fetal mortality and morbidity observed (114). This highlights the need for further research to identify an optimum timing to begin surveillance for placental insufficiencies using ultrasound Doppler measurements to ensure cases are detected as early as possible and the potential to carry out treatment at an earlier timepoint to optimise fetal outcomes.

2.4.5 Induction of labour and intrapartum care

The guidance on intrapartum management in twins is sparse. Published guidance tends to focus on antenatal issues and those that address intrapartum management tend to lack detail and clarity. This reflects the lack of studies proving effective management strategies. This is most apparent in the lack of guidance on induction of labour. Like singleton pregnancies twin pregnancies are often induced due to maternal reasons such as pre-eclampsia or fetal indications including reduced fetal movements and FGR (115). However, in the guidelines we found there was little to no information

particularly regarding the timing of when labour should be induced, the best induction agent for a twin pregnancy, or guidance on the use of oxytocin to accelerate labour and the dosing of this. For an intervention that is very common in twin pregnancy, high-quality evidence to support recommendations is needed. If anything, this highlights the lack of confidence and presence of hesitancy surrounding vaginal birth in twins.

This reluctance is also exemplified by the paucity of advice on managing a vaginal delivery, including fetal monitoring in labour, preferred methods of analgesia, how to stabilise the position of the second fetus and the optimal inter-twin delivery interval. Lack of defined timings and clear management strategies for the delivery of DC and MCDA twins may lead to a discontinuity of care and variable outcomes for women and their fetuses. Options for how women are managed and their outcomes are dependent on the hospital they choose to book at and the confidence of the obstetric and midwifery team in managing twin pregnancies.

2.5 Conclusion

20 published guidelines from 15 countries were identified. Consensus was evident in many aspects of antenatal care for twins; determination of chorionicity, anomaly scan timing and screening for TTTS. There was some variation in precise timing of surveillance and whether cervical length screening should be included. Intrapartum advice demonstrates an evidence gap in timing and mode of delivery. Intrapartum care including fetal monitoring and management of the second twin would benefit from clear guidance.

Chapter 3: Induction of labor between 36 +0 weeks and 40+6 weeks in twins: a systematic review of literature

3.1 Introduction

Around half of twin pregnancies do not reach full term, and are born prematurely (42). This is one of the main contributing factors to the increased rate of morbidity seen in twins compared to singleton pregnancies (116). In those that reach full term, there is on-going debate as to the optimal timing and method of delivery.

Generally, increased gestational age at delivery is associated with decreased perinatal and neonatal mortality (46). However, this has to be balanced against the simultaneous rise in risk of still birth between 37 and 38 weeks gestation (38, 46) . This balance is reflected in current UK NICE guidance which recommends offering 'planned birth' from 37^{+0} weeks for DCDA twins, 36^{+0} weeks for uncomplicated MCDA twins and between 32^{+0} and 33^{+6} weeks in MCMA twins (49). Both elective caesarean section and planned vaginal delivery are deemed 'safe choices' by NICE if the pregnancy is uncomplicated, the leading twin is cephalic, there are no contraindications to labour and there is no significant size discordance however there is a lack of clarity as to the preferential mode of delivery (49).

Many factors contribute to the decision on mode and timing of delivery, however one of the foremost is the outcomes for the neonates; ensuring a safe delivery of both fetuses with limited complications. These decisions should be informed, drawing on information on the risks each method of delivery poses, the risk of intrapartum fetal death or neonatal death, admission to neonatal intensive care (NICU) and requiring ventilatory support as well as other complications.

A 2014 Cochrane review by *Dodd et al* aimed to assess elective delivery at 37 weeks gestation versus expectant management in uncomplicated twin pregnancies with cesarean section, perinatal and maternal death or morbidity as the primary outcomes. They identified two randomized control trials and found there to be no increased risk of harm associated with elective delivery at 37 weeks. However, they also concluded that data is limited due to a lack of clinical equipoise allowing randomization to delivery at a later gestational age (117).

More recently in 2015 *Saccone et al* conducted a systematic review and meta-analysis evaluating the effects of planned delivery at 37 weeks gestation compared to expectant management in women pregnant with twins. Their primary outcome was the rate of cesarean section with secondary outcomes including maternal and neonatal morbidity and mortality. They concluded that there was no difference in rates of cesarean section with planned delivery at 37 weeks being associated with a lower risk of serious adverse infant outcomes (118).

It is clear that previous reviews lack power from small sample size; the review by *Saccone et al* totaled 271 participants from two identified trials, one of which was included in the review by Dodd (118). Given this review has now been published for at least five years, new data may be available. Furthermore, there was no stratification by chorionicity in either metanalysis and prioritization of cesarean section as the primary outcome should be questioned. Those involved in the mode of delivery decision will be concerned about the safety of the fetuses, ensuring their delivery is without adverse outcomes and the need long-term medical input rather than the need for an alternative delivery method.

To examine the effect of induction of labour or expectant management on perinatal and neonatal outcomes in term twin pregnancies, a further review of literature focusing on outcomes of clinical importance to women pregnant with twins and the clinicians involved in their care is required.

3.2 Aims

The aim of the systematic review was to assess the outcomes of elective induction of labour by any method between 36^{+0} and 40^{+6} weeks gestation compared to standard care (spontaneous labour or elective cesarean section) in women pregnant with twins.

The primary outcome is intrapartum fetal deaths and early neonatal deaths (death between 0-7 days after birth). The secondary outcome is neonatal morbidity defined by the following outcomes: infants admitted to NICU (total days on NICU recorded), use of surfactant, ventilator days, oxygen dependency (at 28 days and 36 weeks), any intraventricular haemorrhage (Grade 1-4), necrotizing enterocolitis and need for neonatal/paediatric follow up.

3.3 Methods

We decided to include both randomised control trials (RCTs) and observational studies in this review to provide the most comprehensive assessment of existing literature. We used identical search strategies and data extraction methods for each study type with separate risk of bias analyses.

3.3.1 Search Strategy

We conducted systematic literature searches using the databases MedLine, Academic Search Complete, CINAHL, PROSPERO and Cochrane between 13-18th October 2021. In each search a combination of the following terms was used 'Induction of labour' OR 'induction of labor' AND 'Twin pregnancy' OR 'pregnancy, multiple'.

We excluded search results not in the English language, small studies with <10 participants and decided to focus on data produced in the last two decades so we excluded papers published prior to 2001.

We then used the following MeSH terms to further refine our searches: 'pregnancy, multiple', 'pregnancy, twin', 'cesarean section', 'labour, induced', 'delivery, obstetric' and 'twins'. The papers that remained after removal of duplicates were then screened for relevance by title and abstract. Those deemed relevant after screening were uploaded to the systematic review software Rayyan

(119) where they were then full text screened for eligibility by two reviewers, any conflict was resolved through discussion and where consensus could not be reached disagreements were resolved by a third senior reviewer.

3.3.2 Risk of bias analysis

After selecting eligible papers, we conducted a risk of bias assessment using the Risk of Bias tool for randomised trials (ROB-II) (120) for RCTs and the Newcastle Ottowa quality assessment scale for observational studies (121). These tools looked at the risk of bias arising from selection of the study cohort, the randomisation process, missing outcome data, measurement of the outcome and selection of reported results. This was completed by one reviewer, discussed and agreed upon with two other reviewers.

3.3.3 Data extraction

Data from the included studies were extracted using a standardised data collection tool (figure 20) we developed. The data collected included the following:

- Study design
- Population size and demographics
- Number of vaginal deliveries and caesarean sections from IOL and expectant management groups
- Number of intrapartum and early neonatal deaths in each group
- Neonatal outcomes in each group

Title	Year	Study design	Inclusion Criteria	Exclusion Criteria	Number of sets of twins	Number of MC	Number of DC	Number for IOL	Number for spontaneous delivery/ elective c-section	Indication for IOL	Methods of Induction	Number vaginal deliveries from IOL

Number C-sections from IOL	Number of combined delivery from IOL	Number vaginal deliveries from spontaneous/ elective c-section	Number C-sections from spontaneous/ elective c-section	Number of combined delivery from spontaneous/ elective c-section	Number of intra-partum fetal deaths IOL	Number of perinatal death IOL	Number of intrapartum deaths spontaneous/ elective c-section	Number of perinatal deaths spontaneous/ elective c-section	Number of Neonatal morbidity IOL	Number of Neonatal morbidity spontaneous labour	Admissions to NICU IOL	Admissions to NICU spontaneous labour	Use of Surfactant IOL

Use of Surfactant Spontaneous/ elective c-section	Ventilator Days IOL	Ventilator Days Spontaneous/ elective c-section	Oxygen Dependancy IOL	Oxygen Dependancy Spontaneous/ elective c-section	Intraventricular Haemorrhage IOL	Intraventricular Haemorrhage Spontaneous/ elective c-section	Necrotising enterocolitis IOL	Necrotising enterocolitis Spontaneous/ elective c-section	Need for neonatal/paediatric follow up IOL	Need for neonatal/paediatric follow up Spontaneous/ electvie c-section	Conclusions

Figure 20: *The data collection tool used to collate information from papers included in the systematic review*

(MC: monochorionic, DC: dichorionic, IOL: induction of labour, NICU: neonatal intensive care unit)

3.4 Results

3.4.1 Study Selection

Our searches produced 3,476 results from six databases (MedLine, Academic Search Complete, CINAHL, PROSPERO and Cochrane). After applying the exclusion criteria, MESH terms and removing duplicates there were 545 papers for title and abstract review. This screening removed 522 non-relevant papers leaving 22 papers for full text review. Full text review identified 5 papers for inclusion in the review which was reduced to 4 as the authors of one of the papers were unable to provide full outcomes. They had published pooled outcomes with a larger gestational age range than we had planned to analyse and were unfortunately unable to provide their original data for us to analyse within the time period we required. The reasons for exclusion at full-text review were singleton pregnancies (n=5), inclusion of pregnancies $<36^{+0}$ weeks gestation (n=5), no data on gestational age (n=1), not assessing outcomes of interest (n=5), meta-analysis (n=1). Figure 21 illustrates the search and study selection.

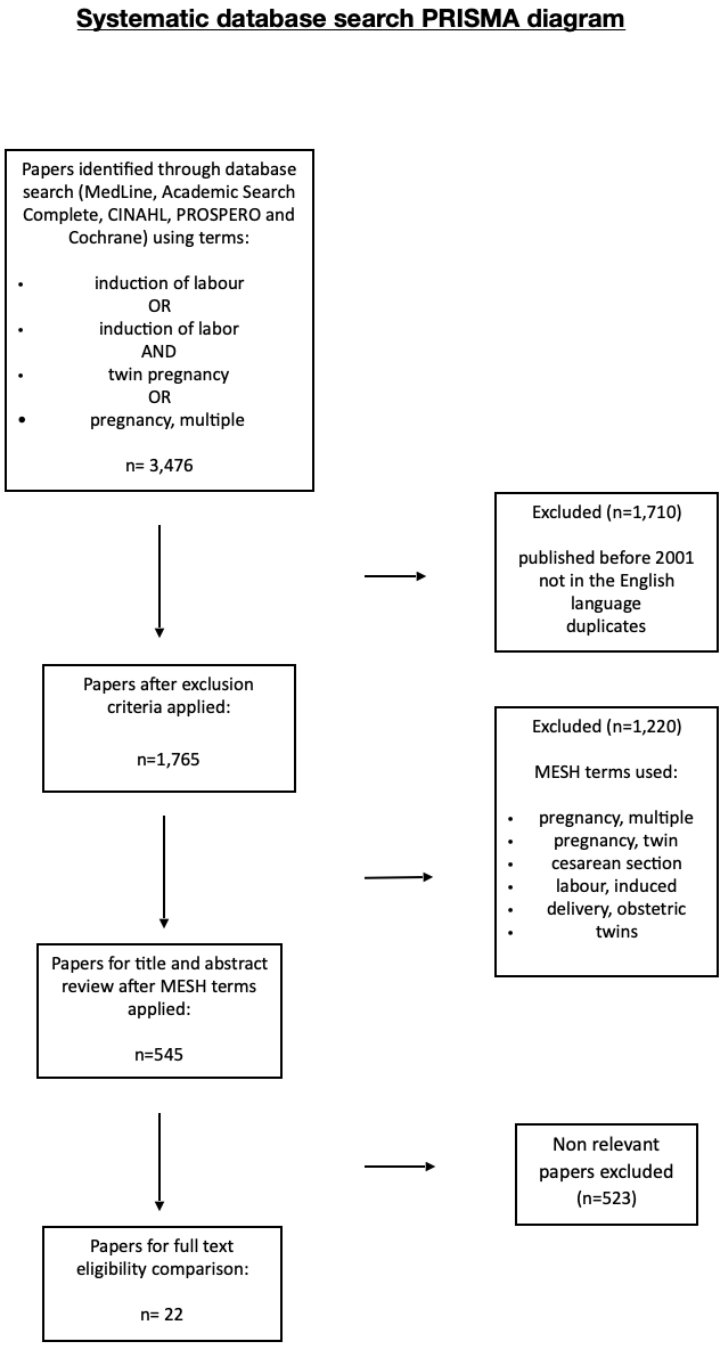

Figure 21: *A PRISMA diagram summarizing the systematic search and study selection.*

3.4.2 Quality of studies

The studies we included were 3 observational studies and 1 randomised control trial. We used the Newcastle Ottowa scale (121) for the observational studies and the ROB-II tool (120) for the RCT. For the Newcastle Ottowa scale (121) a score of 7-9 has a low risk of bias with 9 being the highest achievable score, a score of 4-6 has a moderate risk of bias and 0-3 has high risk of bias. All observational studies were judged to have a low risk of bias with two studies scoring 8/9 and one 7/9. The reasons for dropping points were representativeness of the exposed cohort due to small population size and assessment of the outcome by record linkage.

The ROB-II tool (120) aids judgement of risk of bias on a scale of low risk of bias, some concerns and high risk of bias. The one RCT we included had some concerns of bias in the deviations from intended interventions domain however overall, we scored judged this study to be low risk of bias due to the inability to prevent deviations from intended intervention (i.e emergency caesarean section in a life-threatening situation in a patient intended to deliver by planned vaginal delivery). The results of the risk of bias assessments are shown in table 3 and figure 22.

Table 3: *A table displaying the Newcastle Ottowa Risk of bias assessment results from the included observational studies.*

Author (date)	**Selection of Participants (max score: 4)**	**Comparability (max score: 2)**	**Outcome (max score: 3)**	**Total score:**	**Risk of Bias:**
Harle et al (2002)	3	2	3	8	Low
Tavares et al (2017)	3	2	2	7	Low
Zafman et al (2020)	4	2	2	8	Low

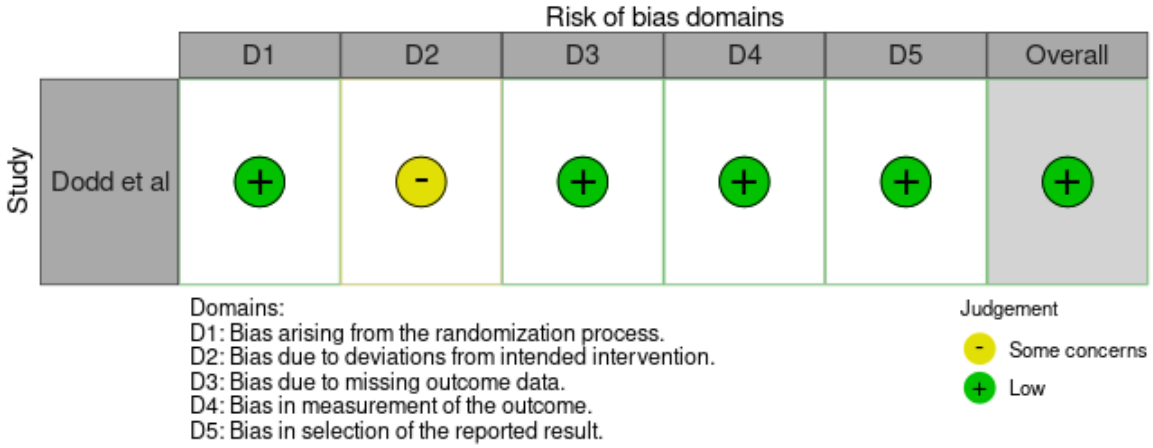

Figure 22: *The ROB-II risk of bias assessment results for the included RCT study.*

3.4.3 Study Characteristics

All of the studies we included had a different design and were from different countries. Three of the studies included both DC and MC twins with one study not reporting chorionicity. All four of the studies assessed intrapartum fetal deaths, perinatal deaths and general neonatal morbidity. Three studies assessed neonatal morbidity further by looking at NICU admissions with two studies looking at cases of necrotising enterocolitis and one at cases of intraventricular haemorrhages. The characteristics of each study are summarised in table 4.

Table 4: *A table summarizing the characteristics of studies included in the systematic review. (IOL: induction of labour, DC: dichorionic, MC: monochorionic)*

Authors	Country	Years of study	Study design	Total population	Number for IOL	Number for standard care	Number of DC	Number of MC	Outcomes assessed
Dodd *et al (122)*	Australia	2003-2010	RCT	235	116	119	193	40	· Intrapartum fetal deaths · Perinatal deaths · Neonatal morbidity
Tavares *et al (123)*	Portugal	2007-2011	Prospective cohort study	75	33	42	62	13	· Intrapartum fetal deaths · Perinatal deaths

									· Neonatal morbidity
Zafman *et al*	USA	2005-2018	Retrospective cohort study	298	159	139	257	41	- Intrapartum fetal deaths - Perinatal deaths - Neonatal morbidity
Harle *et al*	France	1990-1996	Case control study	81	36	45	-	-	- Intrapartum fetal deaths - Perinatal deaths - Neonatal morbidity

3.4.4 Results of studies

From the studies we included all four reported our primary outcomes; intrapartum fetal deaths and early neonatal deaths. Neonatal adverse outcomes were also reported by all four studies. Three of the studies reported number of NICU admissions with a maximum of two studies reporting any other specific neonatal outcomes. These results are displayed in table 5.

Table 5: *A table displaying the results from the studies included in the systematic review. (NICU: neonatal intensive care unit, OR: odds ratio)*

Outcomes	**Study**	**Number of participants**		**OR (95% CI)**	**Risk Ratio**
		Induction of labour	**Expectant management**		
Intrapartum fetal deaths	Dodd (2012)	0/116	0/119	-	-
	Harle (2002)	0/36	0/45	-	-
	Tavares (2017)	0/36	0/42	-	-
	Zafman (2020)	0/159	0/139	-	-
Early neonatal deaths	Dodd (2012)	0/116	1/119	0.34 (0.01-8.48)	0.34
	Harle (2002)	0/36	0/45	-	-
	Tavares (2017)	0/36	0/42	-	-
	Zafman (2020)	0/159	0/139	-	-

Any adverse neonatal outcomes	Dodd (2012)	11/116	28/119	0.40 (0.19-0.84)	0.40
	Harle (2002)	22/36	24/45	1.15 (0.55-2.37)	1.15
	Tavares (2017)	4/36	3/42	1.55 (0.32-7.42)	1.55
	Zafman (2020)	18/159	7/139	2.25 (0.91-5.54)	2.25
Admissions to NICU	Dodd (2012)	2/116	2/119	1.02 (0.14- 7.40)	1.02
	Harle (2002)	22/36	24/45	1.15 (0.55-2.37)	1.15
	Zafman (2020)	16/159	7/139	1.99 (0.79-4.29)	1.91
Use of surfactant	Not reported				
Ventilator days	Not reported				
Oxygen dependency	Not reported				
Intraventricular haemorrhage	Zafman (2020)	0/159	0/139	-	-
Necrotising enterocolitis	Dodd (2012)	0/116	0/119	-	-
	Zafman (2020)	0/159	0/139	-	-
Need for paediatric follow up	Not reported				

Data are given as n/total study participants, Odds Ratio (95% CI) or Risk Ratio.

3.4.4.1 Any adverse neonatal outcomes

Three of the studies demonstrated greater odds of any adverse neonatal outcomes in the IOL group compared to standard care. However, these were not significant and all had wide confidence intervals demonstrating uncertainty over this finding. Additionally, the other study found the converse, demonstrating higher odds of neonatal adverse outcomes in the standard care group. Overall, there is a clear lack of certainty for this outcome making it difficult to draw any conclusions.

3.4.4.2 Admissions to NICU

All three studies that reported admissions to NICU found greater odds of this occurring in the IOL group. However, again there were wide confidence intervals crossing the line of no effect so these findings lack significance.

3.4.4.3 Other outcomes

The other outcomes reported by the studies, including our primary outcomes of intrapartum fetal deaths and early neonatal deaths, either had no or very few events meaning that odds ratios were not estimable. Therefore, conclusions on the effect of IOL versus standard care on these outcomes cannot be drawn.

3.5 Discussion

3.5.1 Findings

The aim of this review was to assess the outcomes of elective induction of labour by any method between 36^{+0} and 40^{+6} weeks gestation compared to standard care (spontaneous labour or elective caesarean section) in women pregnant with twins. We identified four studies that reported our outcomes, all of which looked at intrapartum fetal deaths, early neonatal deaths and adverse neonatal outcomes. Three studies reported admissions to NICU, two looked at cases of necrotising enterocolitis and one reported events of intraventricular haemorrhage. We found the data to be insufficient to report on important outcomes and so were unable to form any definitive conclusions over the management plan that has improved outcomes for women pregnant with twins at term.

3.5.2 Current Literature

Our findings reflect those of Dodd's 2014 Cochrane review which concluded there was insufficient data to detect their outcomes of caesarean section, perinatal and maternal mortality when assessing elective delivery at 37 weeks versus expectant management in twin pregnancies (117). We identified more studies due to the inclusion of observational studies and the time since their review however we also found the data insufficient to draw conclusions on the outcomes. It would be expected that

in just under 20 years there would have been enough adequately powered studies conducted in order to assess our outcomes and form conclusions from meta-analysis but this is not the case. Our review has demonstrated that studies comparing induction of labour to standard of care lack continuity, assessing different sets of outcomes in varying populations and study designs. Because of this analysis by systematic review and meta-analysis is difficult. The need for a large-scale, adequately powered study in this area is clear.

An important study to note is the Twin Birth Study - a randomised trial of planned caesarean or vaginal delivery for twin pregnancy (124). This included 2,804 women pregnant with twins between 32^{+0} and 38^{+6} weeks gestation who were randomly assigned to planned caesarean section or planned vaginal delivery, their outcomes were fetal or neonatal death, serious neonatal morbidity and maternal death or serious maternal morbidity. They found there to be no significant difference in the risk of fetal or neonatal death or serious neonatal morbidity when comparing elective caesarean section to planned vaginal delivery (124). This study provided insight into the safety of delivery methods for twin pregnancies and has demonstrated that both methods should be considered when discussing delivery mode in women pregnant with twins with no contraindications to vaginal delivery. However, due to the inclusion of pregnancies from 32^{+0} weeks onwards the findings of the study cannot be directly applied to twin pregnancies at term with the risk of stillbirth between 37-38 weeks gestation potentially not fully accounted for. The Twin Birth Study demonstrates the ability to carry out a study of this size and gives an excellent model upon which further studies in this area could be designed.

3.5.3 Strengths and limitations

A strength of our study is the inclusion of both randomised control trials and observational studies. This allowed us to explore all available data in this area whilst reflecting both real world conditions where decisions and interventions happen as they are needed as well as controlled management that

is able to determine the effects of intervention more rigorously. The decision to exclude one of these study types would have limited the amount of data we were able to obtain, providing less insight into the outcomes.

Additionally, all of the studies we included were found to have an overall low risk of bias. The only area for concern in the RCT highlighted by the ROB-II assessment was deviation from the intended intervention. However, this is difficult to avoid in a study looking at delivery methods as in cases of life-threatening emergency in the planned vaginal delivery group, deviation from intended delivery method is inevitable. Similarly, in the planned caesarean section group if a woman was to go into fast progressing labour before the planned delivery date it may not be clinically feasible to perform a caesarean section. However, this potential for bias is mitigated by the use of intention to treat analysis, where analysis is based on assigned treatment rather than the actual treatment received and therefore avoids this bias.

For the observational studies the low scoring areas were selection of participants and assessment of outcome and these were scored down due to two studies having a smaller population meaning the sample was less representative of the population seen in the community and data for the outcomes being obtained by record linkage rather than independent blind assessment. Overall, the risk of bias for the included studies were low meaning the results produced from each study have high validity.

A limitation of our study is that overall, we had a relatively small sample size with only 692 twin pregnancies included. The studies we included individually had small populations which meant that many of the outcomes could not be determined and for those that were, the certainty was poor.

Because of this we were unable to carry out meta-analysis of the results which prevents us from providing any definitive answers to which management strategy is associated with improved outcomes.

Furthermore, although the varying study types provided us with a range of data and real-world insight a drawback of this is that it can be harder to make comparisons between the studies. Despite including

three observational studies all of these had a different design, one case-control and two cohort studies, one prospective and one retrospective. All four studies were also conducted in different countries meaning that practices and norms are likely to have high variation between the studies. These factors mean that it is difficult to reliably compare the results of each study between one another and any suggested findings should be taken with caution.

3.5.4 Future research

Our review has clearly demonstrated the need for further studies assessing the outcomes of IOL versus standard care for women pregnant with twins at term, particularly DCDA twins which are more frequently delivered at later gestations. To investigate this further a large-scale, multicentre randomised control trial, similar to the Twin Birth Study should be conducted. Neonatal core outcomes should be agreed and include neonatal morbidity defined by NICU admission, days on NICU, oxygen dependency at 28 days and 36 weeks, necrotising enterocolitis, retinopathy of prematurity, intracranial haemorrhage and use of surfactant. The inclusion criteria would be women pregnant with twins between 36^{+0} – 37^{+0} weeks gestation and they would be excluded based on contraindications to vaginal delivery such as non-cephalic presentation of twin 1, lethal fetal anomalies, maternal contraindications to labour, monoamniotic twins. After being included in the study the women would be randomised to one of two groups, induction of labour at 37^{+0} weeks or standard care where the women are closely monitored until they go into spontaneous labour or are given a caesarean section at the latest safe date. An intention to treat analysis would be used to mitigate any potential bias from deviations from intended intervention. Data would be collected on antenatal maternal and fetal characteristics, outcomes of labour and delivery and the neonatal outcomes previously mentioned. These would be analysed to determine any statistical significance. In order to detect the difference between standard care and induction of labour the study would need to be adequately powered and sample size calculations would be performed in the study design stage to ensure this.

A study of this kind would provide greatly needed clarity to this aspect of management of twin pregnancies however we appreciate that planning and carrying out such a study is not a simple task and that there is value in the use of other methods of data collection. For example, large comprehensive databases can provide great depth of information on outcomes of treatments and intervention. Utilising these may be another solution to provide clarity to this aspect of management of twin pregnancies and help clinicians to fully inform their patients on the options they have for delivery at term.

3.6 Conclusions

Our systematic review assessing the outcomes of induction of labour versus standard care in women pregnant with twins between 36^{+0} and 40^{+6} weeks gestation found there is insufficient data from good quality studies to identify any significant findings. We have highlighted the poor base of evidence in this area and demonstrated the need and outlined a plan for further large-scale studies, in order to provide clarity over the safest management strategy for women pregnant with twins at term.

Chapter 4: A retrospective cohort study assessing intrapartum outcomes in twins at Liverpool Women's Hospital from 2010-2020

4.1 Introduction

Twin pregnancies are often complex (21), involving specialist medical input from the identification of two fetuses, throughout the pregnancy and during delivery. Many women pregnant with twins will opt for a caesarean delivery often due to the perceived risk of a vaginal twin delivery (85, 125). In some cases, there is little choice in the matter due to circumstances contraindicating vaginal delivery such as MCMA twins, non-cephalic leading twin (85) or obstetric emergencies requiring immediate delivery. For these reasons the rate of caesarean delivery in twins is around 50% (126). For those considering a vaginal twin delivery, counselling on the risks involved should take place, including the potential need for an emergency caesarean section of one or both twins, instrumental intervention and the complexity of delivering the second twin (85). Follow up from the *Twin birth Study* (124), a multi-centre, international randomised control trial comparing outcomes of planned vaginal delivery with planned caesarean section, questioned the women who participated on their opinions of the trial. One of the main themes from the responses was the importance of being involved in the decision process of their birth and lack of this in the study (127). This highlights the need to include and involve women pregnant with twins in the conversations surrounding birth options, adequately informing them with information they can understand. For this to happen, evidence on the chance of successful vaginal delivery and potential adverse intrapartum and neonatal outcomes has to exist to inform guidance and translate into the care given and decisions made by healthcare professionals. Our review of international guidance on the management of multiple pregnancy has highlighted the paucity of advice on intrapartum care and lack of consensus in timing and mode of delivery.

A 2018 retrospective cohort study by *Schachter-safrai et al* included 1070 women with twin pregnancies who underwent trial of labour over 12 years. They aimed to identify risk factors for caesarean delivery as well as adverse neonatal outcomes. Their cohort had a success of vaginal delivery rate of 88.3% and identified nulliparity and non-cephalic presentation of the second twin to

be independently associated with caesarean delivery of both twins (128). This study provides helpful insight into factors impacting the success of vaginal delivery however, there is a lack of data on instrumental deliveries, an aspect of vaginal twin delivery that can be clinically challenging as well as important to include in patient counselling. Furthermore, there is a lack analysis of further maternal demographics and intrapartum aspects that could predict successful or unsuccessful vaginal delivery. Similar findings were observed more recently in *Ylilehto et al's* 2020 retrospective cohort study which sought to highlight risk factors associated with intrapartum caesarean section in diamniotic twin pregnancies. In 581 pregnancies that attempted trial of labour the rate of successful vaginal with a cephalic first twin was 82.8% and 60.0% in those where twin one was breech. They identified IVF pregnancy, nulliparity, induction of labour and non-cephalic first or second twin as increased risks for intrapartum caesarean section (129). This further emphasises the impact of nulliparity and non-cephalic presentation on successful vaginal delivery in twins. However, again there is no investigation of intrapartum aspects such as Bishop's score, use of oxytocin to augment labour and epidural anaesthesia which may influence the success of vaginal delivery.

Current literature has improved the understanding of circumstances which may be unfavourable for vaginal delivery of both twins. The relative infrequency of twin pregnancies, particularly those attempting vaginal delivery, mean that studies require years of data to be adequately powered, for this reason there is limited evidence in this area. Our retrospective cohort study aims to add to the existing evidence base and address the lack of analysis into intrapartum predictors of successful vaginal delivery.

4.2 Aims

The primary aim of this study is to identify predictors of successful vaginal delivery in twin pregnancies. Our secondary aim is to highlight predictors of adverse neonatal outcomes in vaginal delivery of twins.

4.3 Methods

4.3.1 Data collection

A database stored at Liverpool Women's Hospital (LWH) contains information on twin pregnancies booked and delivered at the hospital from 2010-2020. This currently contains data on maternal demographics, onset of labour, delivery method and neonatal outcomes. To explore predictors of successful vaginal delivery, further information on intrapartum outcomes needed to be collected. This includes fetal presentation, method of induction of labour, use of epidural anaesthesia, use of oxytocin, intertwin delivery interval, estimated blood loss and $3^{rd}/4^{th}$ degree tears. To collect this data, information was extracted from historical patient records using Meditech software. Data extracted were entered into the existing database.

It was decided to focus on twin pregnancies, excluding any higher order multiple pregnancies due to the infrequency of these and the likelihood that they would be delivered by elective caesarean section, not through labour and vaginal delivery. We also decided to focus on twin pregnancies at term, ≥36 weeks gestation, to understand the chance of successful vaginal delivery in this population, uncomplicated by the additional risks of pre-term labour.

The LWH multiple pregnancy guidance is a document used by clinicians working at LWH caring for women with multiple pregnancies, it is used as a guide to inform management and is based upon data collected from LWH. This guidance states that vaginal delivery can be anticipated if twin 1 is in

cephalic presentation and in the absence of any other obstetrics or fetal complications. In the case where twin 1 is breech, the LWH guidance suggests that caesarean section should be performed unless vaginal delivery is imminent. Intrapartum analgesia is deemed a matter of choice, it is stated that epidural analgesia may have advantages in aiding manipulation of the second twin however maternal choice is respected (130). For the delivery of the second twin the guidance recommends that this should be achieved within 30 minutes and in the case where twin 2 is non-cephalic management is at the discretion of senior clinicians. However, manoeuvres such as external cephalic version and internal podalic version should be considered and where these are not possible caesarean delivery should take place (130).

4.3.2 Statistical analysis

To identify potential predictors of successful vaginal delivery in twin pregnancies we looked at women who were undergoing a trial of labour – either spontaneous labour or induction of labour. We excluded any of the twin pregnancies who had an elective caesarean section, non-labouring emergency caesarean section, were MCMA or had a gestational age <36 weeks.

To identify potential predictors of successful vaginal delivery in twin pregnancies we analysed maternal and fetal demographics as well as clinical factors. The primary outcome was vaginal delivery of both twins where vaginal delivery can be spontaneous, vaginal breech extraction or instrumental delivery using either non-rotational forceps or ventouse.

We initially selected a range of variables to include in the pool of potential predictors. These were: chorionicity, fertility treatment, parity, previous mode of delivery, maternal age, BMI, ethnicity, duration of gestation, onset of labour, bishop score, presentation of twin 1, presentation of twin 2, use of oxytocin and epidural usage. Univariable modelling was then conducted to identify which of

these variables were statistically significant and able to be used in multivariable analysis to develop a clinical model to predict the success of vaginal delivery in twin pregnancies. We decided to conduct a further separate prediction analysis for nulliparous women to assess whether there were different variables impacting success of vaginal delivery in this sub-cohort.

All statistical analysis was completed by Dr Laura Bonnet, Lecturer in Medical Statistics.

4.3.2.1 Univariable modelling

For the univariable modelling logistic regression analysis was carried out for each variable. Continuous variables were assessed via fraction polynomials.

4.3.2.2 Multivariable modelling

To carry out the multivariable analysis multiple imputation via chained equations was undertaken, 20 imputed datasets were created using predictive mean matching. Variables were selected for inclusion in the final model via backwards selection with a p-value of 0.10 and featured in at least 10 of the 20 imputed models. Measures of model performance were calculated for the final model. Non-parametric bootstrapping was used to estimate optimising and examine the stability of the model.

4.4 Results

Data was collected on 1,579 twin pregnancies resulting in 3,140 babies delivered at LWH between January 2010 and November 2020. 1193 of these were DCDA, 369 were MCDA and 17 were MCMA. 388 went into spontaneous labour, 464 had induction of labour, 308 had an elective caesarean section and 419 had an emergency caesarean section.

4.4.1 Maternal demographics of the overall cohort

The median age of our overall cohort before exclusions was 32 and they were primarily Caucasian with some Black and Asian participants, reflecting the Liverpool population. The average BMI was 26.5 and 93.4% (n=1,474) were non-smokers. There was a fairly equal split in parity with 53.4% (n=842) of women multiparous and 31.6% (n=499) had received fertility treatment (IVF, ICSI,IUI, Artificial insemination donor or Clomiphene). The majority of pregnancies were DCDA (75.5% n=1193), 23.4% (n=269) were MCDA and 1.1% (n=17) were MCMA. Table 6 displays these results.

Table 6: *A results table displaying the maternal demographics of our overall cohort (BMI: body mass index, DCDA: dichorionic diamniotic, MCDA: monochorionic monoamniotic, MCMA: monochorionic monoamniotic)*

Demographic	**Number of women:** *Data are presented as n (%), median (IQR) or mean (SD)*
Age:	32 (8)
Ethnicity:	
· *Caucasian:*	1,397 (88.5%)
· *Black:*	51 (3.2%)
· *Asian:*	44 (2.8%)
· *Other/Not stated:*	87 (5.5%)
BMI:	26.5 (16.7-53.6)
Smoker:	
· *Yes:*	105 (6.6%)
Parity:	
· *Parous:*	842 (53.4%)

· *Nulliparous:*	737 (46.6%)
Fertility treatment:	
· *Yes:*	499 (31.6%)
· *No:*	1,067 (67.6%)
· *Not stated:*	13 (0.8%)
Chorionicity & Amnionicity:	
· *DCDA:*	1193 (75.5%)
· *MCDA:*	369 (23.4%)
· *MCMA:*	17 (1.1%)

Data are given as n (%), median (IQR) or mean (SD).

4.4.2 Intrapartum outcomes

The median gestation at delivery was 36^{+2} weeks. 29.4% (n=464) of women had their labour induced, 25.9% (n=410) did not labour and had an elective caesarean section, 24.6% (n=388) went into spontaneous labour and 20.1% (n=317) had an emergency caesarean section. In those that attempted a vaginal delivery 67.0% (n=335) had a successful vaginal delivery of both twins and 4.6% (n=23) had a vaginal delivery of the leading twin only. 182 women had an instrumental delivery, 13.0% (n=65) were for the leading twin only, 16.2% (n=81) were for twin 2 only and 7.2% (n=36) for both twins. Almost half of the women attempting vaginal delivery had epidural anaesthesia and 37.8% (n=322) received oxytocin to augment labour. The median estimated blood loss was 600ml and 3 (0.8%) women had 3rd or 4th degree tears.

Table 7: *A results table summarizing the intrapartum outcomes of our cohort.*

Intrapartum Outcome	**Number of women** *Data are presented as n (%) or median (IQR)*
Gestation at Delivery:	36 (3)
Onset of Labour:	
· *Induction of labour*	464 (29.4%)
· *Non-labouring c-section:*	410 (25.9%)
· *Spontaneous:*	388 (24.6%)
· *Emergency c-section spinal:*	308 (19.5%)
· *Emergency c-section general:*	9 (0.6%)
Vaginal Delivery:	
· *Vaginal Delivery of 2 twins:*	335 (67.0%)
· *Vaginal Delivery of 1 twin:*	23 (4.6%)
Instrumental delivery:	
· *Twin 1 only:*	65 (13.0%)
· *Twin 2 only:*	81 (16.2%)
· *Both twins:*	36 (7.2%)
Use of epidural:	421 (49.4%)
Use of oxytocin:	322 (37.8%)
Estimated blood loss:	600 (400)
3rd/4th degree tear:	3 (0.8%)

Data are given as n (%) or median (IQR)

4.4.3 Neonatal outcomes

3,158 births were reported, of these 98.1% (n=3,097) were live births and 1.3% (n=43) were still births. 47.7% (n=1,507) were female and there was a median birth weight of 2375g. 3.9% (n=125) of neonates had an APGAR score <7 at 5 minutes and 2.9% (n=92) had a cord pH ≤7.10 indicating fetal acidosis. 42.4% (n=1,340) of neonates were admitted to neonatal intensive care (NICU), of these 14.7% (n=463) were affected by respiratory conditions including Respiratory distress syndrome (RDS), Transient tachypnoea of the new-born (TTN), Persistent pulmonary hypertension of the new-born (PPHTN) and Bronchopulmonary dysplasia (BPD). 4.6% (n=146) required administration of surfactant and 5.4% (n=169) were requiring oxygen at 28 days. There 47 (n=1.5%) cases of New-born sepsis, 37 (1.2%) of Retinopathy of prematurity and 27 (0.9%) cases of Necrotising enterocolitis. 18 (0.6%) neonates had seizures and 3 (0.1%) had hypoxic-ischaemic encephalopathy (HIE). These results are shown in table 8.

Table 8: *A results table summarizing the neonatal outcomes of our cohort (NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, TTN: transient tachypnoea of the new-born, PPHTN: persistent pulmonary hypertension of the new-born, BPD: bronchopulmonary dysplasia, HIE: hypoxic-ischaemic encephalopathy)*

Neonatal Outcome	**Number of Neonates** *Data are presented as n (%) or median (IQR)*
Birth outcome:	
· *Live birth:*	3,097 (98.1%)
· *Still birth:*	43 (1.3%)
· *Not reported:*	18 (0.6%)
Sex:	
· *Female:*	1,507 (47.7%)
Birth weight (g):	2375 (750)
APGAR Score <7 at 5 minutes:	125 (3.9%)
Cord pH ≤7.10:	92 (2.9%)
NICU Admissions:	1,340 (42.4%)
Respiratory morbidity: *(RDS/TTN/PPHTN/BPD)*	463 (14.7%)
Oxygen dependence at 28 days:	169 (5.4%)
Surfactant Use:	146 (4.6%)
Intraventricular Haemorrhage:	65 (2.1%)
New born Sepsis:	47 (1.5%)
Retinopathy of prematurity:	37 (1.2%)
Necrotising enterocolitis:	27 (0.9%)
Seizures:	18 (0.6%)
HIE:	3 (0.1%)

Data are presented as n (%) or median (IQR)

4.4.4 Statistical analysis

After applying our exclusion criteria, we produced a table of patient characteristics (Table 9) for this cohort before going on to complete univariable and multivariable analysis.

Table 9: *A table summarizing the patient characteristics of the cohort included in statistical analysis (DCDA: dichorionic diamniotic, MCDA: monochorionic monoamniotic, NICU: neonatal intensive care unit, BMI: body mass index, SD: standard deviation, IQR: interquartile range)*

Characteristic	Grouping	Vaginal delivery of both twins (n=335)	Not vaginal delivery of both twins (n=165)	NICU admission of at least one twin (n=141)	No NICU admission of either twin (n=359)
Chorionicity	*DCDA*	276 (82)	138 (84)	115 (82)	299 (83)
	MCDA	59 (18)	27 (16)	26 (18)	60 (17)
Fertility treatment	*No*	270 (81)	109 (66)	108 (77)	271 (75)
	Yes	65 (19)	56 (34)	33 (23)	88 (25)
Previous mode of delivery	*Vaginal*	231 (69)	58 (35)	78 (55)	211 (59)
	Not vaginal	2 (1)	9 (5)	4 (3)	7 (2)
	None	102 (30)	98 (60)	59 (42)	141 (39)
Ethnicity	*White*	292 (90)	143 (88)	126 (91)	309 (88)
	Asian	8 (2)	3 (2)	4 (3)	7 (2)
	Black	8 (20)	10 (6)	4 (3)	14 (4)
	Mixed	10 (3)	1 (1)	3 (2)	9 (3)
	Other	8 (2)	6 (4)	2 (1)	11 (3)
	Not provided	*9*	*2*	*2*	*9*
Onset of labour	*Induction*	275 (82)	116 (70)	105 (74)	286 (80)

	Spontaneous	60 (18)	49 (30)	36 (26)	73 (20)
Presentation of twin 1	*Cephalic* *Breech* *Oblique* *Transverse* *Other* *Not known (n=6)*	332 (99) 2 (1) 0 (0) 0 (0) 1 (0)	128 (81) 24 (15) 1 (1) 1 (1) 5 (3)	125 (90) 11 (8) 0 (0) 0 (0) 3 (2)	335 (94) 15 (4) 1 (0) 1 (0) 3 (1)
Presentation of twin 2	*Cephalic* *Breech* *Oblique* *Transverse* *Other* *Not known (n=17)*	209 (63) 112 (34) 1 (0) 5 (2) 6 (2)	78 (52) 52 (35) 2 (1) 10 (7) 7 (5)	78 (57) 47 (35) 2 (1) 7 (5) 2 (1)	209 (60) 117 (34) 1 (0) 8 (2) 11 (3)
Use of oxytocin	*No* *Yes* *Not relevant/missing (n=20)*	175 (52) 159 (48)	80 (55) 66 (45)	76 (57) 58 (43)	179 (52) 167 (48)
Epidural usage	*No* *Yes* *Not relevant/missing (n=25)*	106 (32) 228 (68)	60 (43) 81 (57)	48 (36) 84 (64)	118 (34) 225 (66)
Parity	*0* *1*	102 (30) 134 (40)	99 (60) 33 (20)	59 (42) 48 (34)	142 (40) 119 (33)

	2 *3+*	59 (18) 40 (12)	15 (9) 18 (11)	20 (14) 14 (10)	54 (15) 44 (12)
Bishop Score, median (IQR) *Not relevant/missing (n=135)*		4 (3, 6)	3 (1, 4)	4 (2, 6)	4 (2, 6)
Maternal age, mean (SD)		31.1 (5.5)	32.1 (5.7)	31.6 (5.5)	31.4 (5.6)
BMI, median (IQR) *Missing (n=7)*		24.4 (22.0, 28.9)	25.1 (22.2, 29.7)	25.3 (22.0, 29.2)	24.4 (22.2, 29.2)
Duration of gestation (total days), median (IQR) *Missing (n=7)*		260 (256, 262)	260 (256, 262)	259 (254, 262)	260 (257, 262)

Data are presented as n (%), mean (SD) or median (IQR).

4.4.4.1 Univariable modelling

Univariable modelling found a history of fertility treatment, non-cephalic presentation of twin 1, non-cephalic presentation of twin 2 and spontaneous onset of labour to be negatively associated with successful vaginal delivery. Whilst previous vaginal delivery, epidural usage and increasing Bishop score were positively associated with the outcome. These variables were then used in the multivariable modelling. For the second outcome of admission to NICU the only variable which was significant was duration of gestation, because of this multivariable analysis for this outcome was not carried out. However, it does demonstrate that shorter duration of gestation is significantly associated with admission to NICU. The results of the univariable modelling are displayed in table 10, the results in red or green are statistically significant at the 5% level, those in red are variables which have shown to make successful vaginal delivery less likely and those in green more likely.

Table 10: *A table of the univariable modelling results for the outcome of successful vaginal delivery in both twins and the outcome of admission of at least one twin to NICU. Logistic regression analysis was carried out for each variable. Continuous variables were assessed via fraction polynomials. (DCDA: dichorionic diamniotic, MCDA: monochorionic monoamniotic, NICU: neonatal intensive care unit, OR: odds ratio, BMI: body mass index)*

Predictor	Comparison	Both vaginal, OR (95% CI)	At least one in NICU, OR (95% CI)
Chorionicity	*Intercept*	*0.69 (0.10)*	*-0.95 (0.11)*
	DCDA	1.00	1.00
	MCDA	1.09 (0.66, 1.80)	1.13 (0.68, 1.87)
Fertility treatment	*Intercept*	*0.91 (0.11)*	*-0.92 (0.11)*
	No	1.00	1.00
	Yes	0.47 (0.31, 0.71)	0.94 (0.60, 1.49)
Previous mode of delivery	*Intercept*	*0.04 (0.14)*	*-0.87 (0.16)*
	None	1.00	1.00
	Vaginal	3.83 (2.57, 5.71)	0.88 (0.59, 1.32)
	Not vaginal	0.21 (0.05, 1.01)	1.37 (0.39, 4.84)
Ethnicity	*Intercept*	*0.71 (0.10)*	*-0.90 (0.11)*
	White	1.00	1.00
	Not white	0.96 (0.55, 1.66)	0.74 (0.40, 1.36)
Onset of labour	*Intercept*	*0.86 (0.11)*	*-1.00 (0.11)*
	Induction	1.00	1.00
	Spontaneous	0.52 (0.33, 0.80)	1.34 (0.85, 2.12)
Presentation of twin 1	*Intercept*	*0.95 (0.10)*	*-0.99 (0.10)*
	Cephalic	1.00	1.00

	Not cephalic	0.03 (0.01, 0.10)	1.79 (0.92, 3.47)
Presentation of twin 2	*Intercept*	*0.99 (0.13)*	*-0.99 (0.13)*
	Cephalic	1.00	1.00
	Not cephalic	0.54 (0.37, 0.79)	1.13 (0.76, 1.67)
Use of oxytocin	*Intercept*	*0.78 (0.13)*	*-0.86 (0.14)*
	No	1.00	1.00
	Yes	1.10 (0.75, 1.63)	0.82 (0.55, 1.22)
Epidural usage	*Intercept*	*0.57 (0.16)*	*-0.90 (0.17)*
	No	1.00	1.00
	Yes	1.59 (1.06, 2.39)	0.92 (0.60, 1.40)
Parity	*Intercept*	*0.03 (0.14)*	*-0.88 (0.15)*
	0	1.00	1.00
	1	3.94 (2.46, 6.31)	0.97 (0.62, 1.53)
	2	3.82 (2.03, 7.17)	0.89 (0.49, 1.62)
	3+	2.16 (1.16, 4.01)	0.77 (0.39, 1.50)
Bishop Score *(linear)*	*Intercept*	*-0.61 (0.28)*	*-1.16 (0.28)*
	Per Score	21.67 (7.18, 65.39)	1.21 (0.48, 3.07)
Maternal age *(linear)*	*Intercept*	*1.75 (0.56)*	*-1.20 (0.57)*
	Per year of age	0.97 (0.89, 1.36)	1.01 (0.71, 1.43)
BMI *(linear)*	*Intercept*	*0.73 (0.46)*	*-0.83 (0.48)*
	Per 1 unit increase	1.00 (0.71, 1.40)	1.00 (0.70, 1.42)
Duration of gestation *(linear)*	*Intercept*	*-1.16 (4.57)*	*12.47 (5.37)*
			0.95 (0.91, 0.99)

	Per 1-day increase	1.01 (0.03, 31.65)	

Data are presented as Odds Ratio (95% CI), those highlighted in green are significantly positively associated with the outcome and those highlighted in red are significantly negatively associated with the outcome.

4.4.4.2 Multivariable modelling

According to the outcomes of the univariable modelling both parity and previous mode of delivery should be included in the model however, because they are highly correlated the model fails to fit properly. Because of this, two models were produced, one without parity and one without previous mode of delivery.

4.4.4.2a Model without parity

The model without parity found that fertility treatment, previous mode of delivery, presentation of the twins, epidural usage and Bishop score were all associated with the outcome of successful vaginal delivery in both twins. Women with a history of fertility treatment and non-cephalic presentation for twin 1 or twin 2 were less likely to achieve the outcome whilst women with a previous vaginal delivery and epidural anaesthesia were more likely to have successful vaginal delivery of both twins. For each unit increase in Bishop score, the chance of vaginal delivery for both babies increased by 26%. These results are shown in table 11. This model had good performance measures and is the most stable out of the two produced. The discrimination of the model, the ability of it to separate between those that will have an event and those that will not can be measured and attributed a value between 0.5-1.0, 0.5 being a low score and 1.0 the perfect score. The discrimination of this model is 0.80 (95% CI 0.75-0.89) meaning that there is good ability of the model to separate between those that do have two vaginal births from those that do not. The

calibration slope and calibration in the large values, other measures of the quality of the model, suggest good calibration and hence a good agreement between the probability of twin successful vaginal deliveries predicted by the model, and the actual outcome. These performance measures are displayed in table 11.

4.4.4.2b Model without previous mode of delivery

The model including parity and without previous mode of delivery had the same findings as the first model with parity of 1 or 2 also associated with increased likelihood of successful vaginal delivery of both twins, Table 11. The discrimination of this model was 0.80 (95% CI 0.73-0.82) again showing good ability of the model to separate between women who have two vaginal births from women who do not. The calibration slope and calibration in the large values suggest good calibration and a good agreement between the probability of two successful vaginal deliveries predicted by the model and the actual outcome, however these values were lower than the previous model, see table 12.

Table 11: *A table of the multivariable modelling results for the outcome of successful vaginal delivery in both twins in the model without parity and the model without previous mode of delivery, analysis was performed using multiple imputation via chained equations, predictive mean matching and backwards selection. (OR: odds ratio, CI: confidence interval)*

Predictor	**Comparison**	**Both vaginal, OR (95% CI)** ***Without parity***	**Both vaginal, OR (95% CI)** ***Without previous mode of delivery***
Intercept	*-0.55 (0.36)*	*-0.48 (0.36)*	12.82 (5.38)
Fertility treatment	*No*	1.00	1.00

	Yes	0.47 (0.28, 0.79)	0.44 (0.26, 0.74)
Previous mode of delivery	*None* *Vaginal* *Not vaginal*	1.00 3.65 (2.18, 6.11) 0.30 (0.05, 1.87)	N/A
Presentation of twin 1	*Cephalic* *Not cephalic*	1.00 0.04 (0.01, 0.16)	1.00 0.03 (0.01, 0.13)
Presentation of twin 2	*Cephalic* *Not cephalic*	1.00 0.57 (0.36, 0.90)	1.00 0.56 (0.36, 0.89)
Epidural usage	*No* *Yes*	1.00 1.79 (1.06, 3.02)	1.00 1.64 (0.96, 2.79)
Parity	*0* *1* *2* *3+*	N/A	1.00 3.78 (2.13, 6.70) 4.10 (1.79, 9.40) 1.88 (0.83, 4.25)
Bishop Score *(linear)*	*Per Score*	1.28 (1.15, 1.44)	1.29 (1.15, 1.45)
Duration of gestation *(linear)*	*Per 1-day increase*	N/A	N/A

Data are presented as Odds Ratio (95% CI), those highlighted in green are predictors shown to increase the chance of successful vaginal delivery and those highlighted in red are predictors shown to decrease the chance of successful vaginal delivery.

Table 12: *A table summarizing the performance measures of the models, analysis was performed using non-parametric bootstrapping.*

	Both vaginal ***Without parity***	**Both vaginal** ***Without mode***
C-statistic	0.82 (0.77, 0.86)	0.81 (0.77, 0.85)
Calibration slope	1.00 (0.81, 1.21)	1.00 (0.81, 1.21)
Calibration in the large	0 (-0.22, 0.22)	0 (-0.22, 0.22)

Data are presented as C-statistic value (95% CI) or Calibration value (95% CI)

4.4.4.3 Analysis of nulliparous women

We conducted a further analysis to separately assess the chance of successful vaginal delivery in nulliparous women. We found the highest chance of success (91%) in women with no previous fertility treatment, cephalic presentation of both twins and a high bishop score and the lowest chance (1%) in women who had previous fertility treatment, non-cephalic presentation of both twins and a Bishop score of 0 (table 13 and figure 22).

Table 13: *A table to show the predicted probability of successful vaginal delivery of both twins in nulliparous women based upon variations of characteristics. Analysis was performed using logistic regression analysis for each variable. Continuous variables were assessed via fraction polynomials.*

Parity	**Previous fertility treatment**	**Presentation of Twin 1**	**Presentation of Twin 2**	**Bishop score**	**Predicted probability of two vaginal deliveries (%, 95% confidence interval)**
0	No	Cephalic	Cephalic	0	39 (35, 44)
0	No	Cephalic	Cephalic	3	56 (52, 61)
0	No	Cephalic	Cephalic	6	72 (68, 76)
0	No	Cephalic	Cephalic	9	84 (81, 87)
0	No	Cephalic	Cephalic	12	91 (89, 94)
0	No	Cephalic	Not cephalic	0	28 (24, 32)
0	No	Cephalic	Not cephalic	3	43 (39, 48)
0	No	Cephalic	Not cephalic	6	60 (56, 65)
0	No	Cephalic	Not cephalic	9	75 (71, 79)

0	No	Cephalic	Not cephalic	12	86 (83, 89)
0	No	Not cephalic	Cephalic	0	3 (2, 5)
0	No	Not cephalic	Cephalic	3	6 (4, 8)
0	No	Not cephalic	Cephalic	6	11 (9, 14)
0	No	Not cephalic	Cephalic	9	20 (17, 24)
0	No	Not cephalic	Cephalic	12	34 (30, 38)
0	No	Not cephalic	Not cephalic	0	2 (1, 3)
0	No	Not cephalic	Not cephalic	3	4 (2, 5)
0	No	Not cephalic	Not cephalic	6	7 (5, 9)
0	No	Not cephalic	Not cephalic	9	13 (10, 16)
0	No	Not cephalic	Not cephalic	12	23 (19, 27)
0	Yes	Cephalic	Cephalic	0	24 (20, 28)
0	Yes	Cephalic	Cephalic	3	38 (34, 43)
0	Yes	Cephalic	Cephalic	6	55 (51, 60)
0	Yes	Cephalic	Cephalic	9	71 (67, 75)
0	Yes	Cephalic	Cephalic	12	83 (80, 86)
0	Yes	Cephalic	Not cephalic	0	16 (12, 19)
0	Yes	Cephalic	Not cephalic	3	27 (23, 31)
0	Yes	Cephalic	Not cephalic	6	42 (38, 47)
0	Yes	Cephalic	Not cephalic	9	59 (55, 64)
0	Yes	Cephalic	Not cephalic	12	74 (71, 78)
0	Yes	Not cephalic	Cephalic	0	2 (0, 3)
0	Yes	Not cephalic	Cephalic	3	3 (2, 5)
0	Yes	Not cephalic	Cephalic	6	6 (4, 8)
0	Yes	Not cephalic	Cephalic	9	11 (8, 14)
0	Yes	Not cephalic	Cephalic	12	20 (16, 23)
0	Yes	Not cephalic	Not cephalic	0	1 (0, 2)
0	Yes	Not cephalic	Not cephalic	3	2 (1, 3)
0	Yes	Not cephalic	Not cephalic	6	4 (2, 5)
0	Yes	Not cephalic	Not cephalic	9	7 (5, 9)
0	Yes	Not cephalic	Not cephalic	12	13 (10, 16)

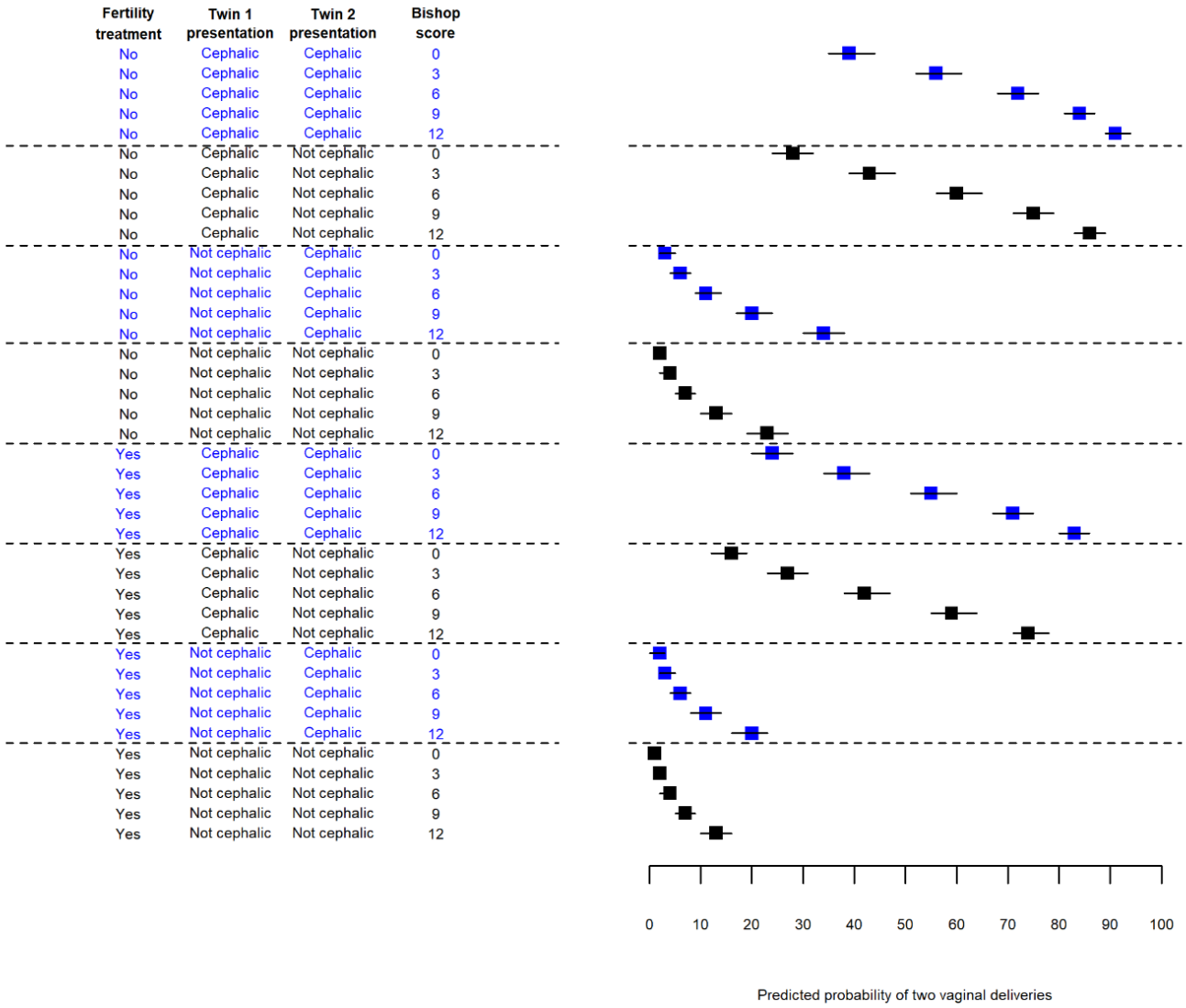

Figure 23: *A graph to show the predicted probability of successful vaginal delivery of both twins in nulliparous women based upon variations of characteristics.*

4.5 Discussion

4.5.1 Findings

Our retrospective cohort study found that women who are multiparous, have had a previous vaginal delivery, have a high Bishop score or who receive epidural anaesthesia during labour are more likely to have a successful vaginal delivery of both twins. We also found that women who have a history of fertility treatment or non-cephalic presentation of twin 1 or twin 2 are less likely to achieve this outcome. It is important to note that this may be due to bias, particularly in the case of women who have undergone fertility treatment where the fetus may be perceived as particularly precious and so interventions and methods perceived as higher risk, but may lead to successful vaginal delivery, are less likely to be offered or accepted. Similarly, in cases of non-cephalic presentation there may be bias due to preference of the clinicians caring for the women in how they choose to manage this scenario. The LWH multiple pregnancy guidance states that where the first twin in non-cephalic, caesarean section should be considered, this is not a strict rule and will be dependent on the clinicians involved however this is important to consider when critically assessing the predictors we have identified.

4.5.2 Existing literature

4.5.2.1 Parity

Our findings that multiparity increases the chance of successful vaginal delivery are supported by and build upon those of a 2011 prospective cohort study assessing predictors of vaginal twin birth (131). This study looked at 441 women pregnant with twins undergoing a trial of labour, their cohort demographics were similar to ours with a median age of 32.7 compared to our 31.6, there was a similar split of chorionicity with 82.8% (n=414) of twin pregnancies in our cohort DCDA compared to

81.4% (n=359). Our cohort had a higher proportion of multiparous women, 59.2% (n=296) compared to 49.0% (n=241). This study demonstrated a rate of successful vaginal delivery of 76% (n=337), slightly higher than our 67% (n=335). Comparable to our results they identified multiparity as a predictor of successful trial of labour and also found this for spontaneous conception (131). These results show that our findings for multiparity are comparable to existing literature, showing good validity. The increased rate of successful vaginal delivery may be partially attributed to their management protocol of regional anaesthesia for twin births which we found to be a predictor of successful vaginal delivery.

4.5.2.2 Fetal presentation

Our findings that women pregnant with twins where twin 2 is non-cephalic are less likely to achieve successful vaginal delivery were not supported by a previous study. This was a retrospective cohort study looking at successful twin vaginal delivery where twin 1 was cephalic and twin 2 either cephalic or non-cephalic. They included 349 patients that underwent trial of labour, 73% (n=296) were cephalic/cephalic and 17% (n=53) were cephalic/non-cephalic and found 85% (n=45) of these had a successful vaginal delivery compared to 70% (n=207) of cephalic/cephalic patients, however this was not statistically significant (132). Despite these findings differing from our own this should be interpreted with caution due to the small and unbalanced cohort of cephalic/non-cephalic patients they included as well as the lack of statistical significance. A recent study by Goffinett looked at 1,467 women with a breech presenting first twin and assessed neonatal mortality and morbidity by planned mode of delivery and found no differences between planned caesarean section and planned vaginal delivery (133). This provides reassurance that vaginal delivery where the first twin is non-cephalic is safe and an option for these women.

4.5.2.3 NICU Admission

We found that duration of gestation is negatively associated with admission to NICU, with those delivering earlier more likely to be admitted. This is a well-known finding due to the effects of prematurity frequently requiring medical intervention after birth (134-136). This demonstrates high validity of this finding and adds to the existing large base of evidence that infants delivered prematurely are likely to have worse outcomes.

4.5.2.4 Other variables

We failed to identify any studies that fully assessed the impact of previous vaginal delivery, Bishop score or use of epidural anaesthesia on the success of vaginal delivery in twins. Many of the studies we came across were investigating predictors of unsuccessful vaginal delivery/caesarean section in twin pregnancies that undergo trial of labour. Whilst seemingly relevant the primary outcome is different to our own and it would be wrong to assume that the predictors for unsuccessful vaginal delivery are inversely correlated to successful vaginal delivery. For this reason, we have not explored the findings of these studies further.

We also did not identify any studies assessing factors associated with success of vaginal delivery for nulliparous women pregnant with twins so therefore we cannot comment on the validity of our findings.

4.5.3 Strengths and limitations

A strength of our study is the size of the cohort. Due to the number of patients we were able to collect data on and include in our analysis our findings are likely to be well representative of the general UK population. Additionally, our split of chorionicity reflects that of what is usually observed in populations of twin pregnancies. For these reasons our findings have good potential applicability

to other twin populations provided we perform external validity testing of the model in a prospective cohort separate from our own twin population as well as other twin cohorts in different centres.

Another strength is the breadth of data we were able to collect for each pregnancy. The record system used at LWH is comprehensive and detailed enabling us to collate data on maternal and fetal demographics as well as intrapartum, perinatal and neonatal outcomes. Overall, we had a low proportion of missing data meaning that we did not have to exclude any patients from the analysis.

A limitation of this study is that it is retrospective, relying on the accurate input of data by health-care staff at the time of the patient's care. Without any way of retrospectively assessing the accuracy of this process this aspect will always be a potential risk for bias and therefore a potential limitation. Furthermore, due to the retrospective nature of our study we have assumed that women who went into spontaneous labour were motivated for a trial of vaginal birth, this assumption is based of knowledge of the management of twin pregnancies at LWH and the conversations that are had around birth choices. However, we can appreciate that this may not be the case in for every woman and therefore may be a source of bias.

Due the design of this study we cannot make any definitive conclusions and ascertain absolute predictors for successful vaginal delivery in twin pregnancies. However, it is known that designing randomised control trials can be a challenge when looking at the management of pregnancy, particularly the intrapartum period, therefore the findings from our retrospective cohort study provide good quality insight and clinically useful findings in this area.

A further drawback of our study is that we were unable to make any conclusions on predictors for adverse neonatal outcomes in vaginal delivery of twin pregnancies. The variables we investigated were not shown to be significant to positively or negatively predict adverse outcomes in neonates. This may mean a larger cohort and further analysis is required to determine significant associations

or simply that the variables we were observing do not have any impact on adverse neonatal outcomes.

4.5.4 Implications

Our findings are clinically important as we have addressed a gap in current literature, identifying multiple characteristics that can predict successful vaginal delivery in twin pregnancies. This will allow clinicians to effectively counsel women pregnant with twins considering the option of a vaginal delivery. Provided that we perform rigorous external validity testing in twin cohorts separate from our own, the model we have developed has the potential for clinicians to be able to input individual data for each woman they manage, producing an individualised prediction of their chance of successful vaginal delivery. This would allow thorough, personalised counselling and informed, joint decision making.

Our review of international guidelines on the management of multiple pregnancy found that advice on the mode of delivery for DCDA and MCDA twins lacked consensus with a range of circumstances in which vaginal delivery was recommended varying. Our findings provide clarity to this area with a set of maternal demographics and clinical scenarios in which successful vaginal delivery is more likely. Utilisation of the model we have developed may help to prevent clinicians from giving patients ambiguous advice on a plan for delivery, which is likely when following current guidance.

4.6 Conclusions

Our findings have shown that women pregnant with twins are more likely to have a successful vaginal delivery of both twins if they are multiparous, have had a previous vaginal delivery, have a high Bishop's score or use epidural anaesthesia. Conversely, women with a history of fertility treatment or with non-cephalic presentation of either twin are less likely to achieve this. We have

developed a clinical prediction model with the potential to allow individual prediction of successful vaginal delivery in twin pregnancies.

Chapter 5: The use of Computerised Cardiotocography to assess fetal wellbeing in twin pregnancies

5.1 Introduction

Fetal wellbeing, throughout pregnancy, and during labour is at the forefront of the minds of the mother, clinicians and those involved in the pregnancy. Assessments of fetal wellbeing begin with routine ultrasound scans in the first two trimesters, to identify chromosomal or structural anomalies as well as observing fetal movements and fetal heartbeat auscultation.

For twin pregnancies ultrasound scans will take place every four weeks from twenty weeks gestation for dichorionic twins and every two weeks from sixteen weeks for monochorionic twins, during these scans additional measurements will be taken including amniotic fluid volumes, and a full range of maternal-fetal Dopplers, to further assess fetal wellbeing (49). At each appointment the woman will be counselled on signs and symptoms to look out for and when to come in to the hospital to be assessed, these symptoms include vaginal bleeding, reduced fetal movements after twenty-four weeks gestation and abdominal pain (93). If a pregnant woman presents to the maternity assessment unit with complications they are likely to undergo a series of tests to assess maternal and fetal wellbeing, if this happens within the third trimester this may include a cardiotocograph (CTG) (137).

A cardiotocograph is an electronic record of fetal heart rate and uterine activity which is detected by two ultrasound transducers, or three in the case of twins, one for each fetus and one for the uterus (137). A paper copy of the reading can be produced which will show a trace for each fetal heart beat and one for uterine activity, this will show the fluctuation of the fetal heart rate and any increases in pressure from the uterus which may reflect contractions (137). Several aspects of the fetal heart rate are assessed during the CTG, including the baseline – the mean fetal heart rate, baseline variability (short term variation) – fluctuations of the fetal heart rate around the baseline, accelerations – quickening of the fetal heart rate and decelerations – slowing of the fetal heart rate (76, 137). The baseline fetal heart rate should be around 110-160 beats per minute and the short-term variation should be greater than 5bpms, deterioration in baseline and reduced variability can indicate hypoxia

and fetal distress. Decelerations can also be indicative of this if they persist after the end of a contraction, known as late decelerations (76).

Analysis of the components of a CTG can be done manually by trained clinicians but is often carried out by a computerised system linked to the transducers. This is overall more objective and reproducible, allowing fast, reliable analysis of the traces and interpretation of more information than can be achieved by a clinician (137). The most widely used system is the Dawes-Redman system of computerised analysis, this analyses features of the CTG including short term variation, accelerations, decelerations, fetal movements and quality of the trace to assess whether the CTG meets the criteria to be a 'reassuring' CTG (137-139). The criteria can be met at any time within 10-60 minutes, if it does not meet by 60 minutes the trace is classed as abnormal and the features causing this are highlighted (138).

The use of computerised CTGs as an assessment of fetal wellbeing is common practice in all pregnancies, in singletons there is a mixed response to their effectiveness. In *Dawes et al's* study investigating the application of computerised fetal heart rate analysis in clinical practice they studied 2869 pregnant women undergoing CTGs randomised computer analysis being concealed or revealed to the clinicians. In cases where the computer analysis was revealed there was evidence of saving time and improvement of record quality. When the computer analysis was concealed and interpretation of the CTG required estimation of the fetal heart rate variation there was observer misinterpretation, questioning the reliability of visual analysis (140). However, a more recent Cochrane review by *Grivell et al* which aimed to assess the effectiveness of antenatal CTG, including computerised analysis, on improving maternal and fetal/neonatal outcomes. They identified six studies including 2105 pregnant women and found no improvement to perinatal mortality, preventable deaths, APGAR score >7 at five minutes or admission to NICU when comparing traditional CTG to no CTG. In comparison of computerised CTG to traditional CTG there was a

significant reduction in perinatal mortality when using computerised CTGS but no difference in preventable deaths or APGAR score >7 at five minutes (137).

Conducting a CTG in a twin pregnancy is not as straightforward as with singletons and presents various challenges, particularly surrounding the accuracy of detecting both fetal heart rates. To form a true assessment fetal wellbeing and produce reliable CTG measurements the heartbeat of each twin must be detected and continuously recorded throughout the duration of the CTG measurement. If this does not happen there is a risk of failing to detect fetal compromise in either fetus. In order to obtain an accurate reading the transducers must be placed on the abdomen over the area of each fetal heart and remain in the correct place throughout the measurement. However, both fetuses are likely to be active and will change position so altering the placement of the transducers to maintain a correct reading is often required. Another challenge is the labelling of the twins. From the first ultrasound scan the fetuses will be labelled as twin 1 or twin 2 based on various features including their site, left/right or upper/lower and other notable features such as sex, size difference and cord insertion site (19). This labelling should be maintained throughout the pregnancy so that each fetus can be monitored individually over time. It is important to continue the same labelling on CTG so that the measurements can be interpreted in line with existing information on the fetuses, for example whether the fetus has a congenital anomaly or selective fetal growth restriction.

The complexity of twin pregnancies and the challenge of using of computerised CTGs to assess twin fetal wellbeing raises the question of how effective these are in detecting fetal distress, indicating intervention and improving adverse outcomes. To the best of our knowledge there is a lack of evidence in this area, therefore this study aims to address this, assessing the use of computerised CTGs in twin pregnancies as an assessment of fetal wellbeing.

5.2 Aims

The aims of this study are to observe the use of computerised CTG in twin pregnancies and assess the correlation of STV and Dawes Redman analysis to fetal wellbeing.

5.3 Methods

5.3.1 Data collection

Using hospital records we identified women pregnant with twins receiving care at Liverpool Women's Hospital (LWH) who had a computerised CTG antenatally between January 2010 and November 2020. We used Meditech software to find records of the CTG reports within patient notes from the Maternal Assessment Unit as well as maternal demographic data from the booking notes. We had previously collected data on delivery neonatal outcomes which we also included.

We collected data on maternal age, ethnicity, BMI, smoking status, chorionicity, complications of pregnancy including hypertensive diseases of pregnancy, selective fetal growth restriction, onset of labour, gestation at delivery and mode of delivery. Data from the CTGs included number of CTGs, gestation at CTG, indication for CTG, STV in twin 1, STV in twin 2, whether Dawes Redman (DR) criteria met for twin 1 and twin 2, time to meet criteria in twin 1 and twin 1 and whether delivery was indicated from the CTG. We collected neonatal outcome data looking at whether the twins were live birth or still birth, their birth weight, sex, 5-minute APGAR score, cord pH, admission to NICU and neonatal morbidity including sepsis, respiratory morbidity and retinopathy of prematurity.

5.4 Results

We identified 265 women pregnant with twins that had undergone at-least one antenatal CTG between January 2010 and November 2020.

5.4.1 Study population

Table 14 summarises the characteristics of the population included in our study. The women were primarily Caucasian, under the age of 40 and multiparous. 78.5% (n=208) had a dichorionic twin pregnancy with 27.2% (n=72) affected complications including hypertensive disorders of pregnancy (HDP), selective fetal growth restriction (sFGR) or gestational diabetes mellitus (GDM).

Table 14: *A table summarizing the patient characteristics of our cohort (BMI: body mass index, DC: dichorionic, MC: monochorionic, HDP: hypertensive disorders of pregnancy, sFGR: selective fetal growth restriction, GDM: gestational diabetes mellitus)*

Demographic	**Number of women** *Data are presented as n (%), median (IQR) or mean (SD)*
Age (years):	32 (8)
Ethnicity:	
· *Caucasian:*	232 (87.5%)
· *Black:*	8 (3.0%)
· *Asian:*	4 (1.5%)
· *Other/Not stated:*	21 (7.9%)
BMI:	26.0 (22.8 – 30.4)
Smoker:	
· *Yes:*	42 (15.8%)
Parity:	
· *Nulliparous:*	102 (38.5%)
Chorionicity:	

· *DC:*	208 (78.5%)
· *MC:*	56 (21.1%)
Complications:	
· *HDP:*	28 (10.6%)
· *sFGR:*	25 (9.4%)
· *GDM:*	19 (7.2%)

Data are presented as n (%), median (IQR) or mean (SD)

5.4.2 CTG characteristics

The women in our study had an average of two cCTGs each throughout their pregnancy, the average gestation at the first cCTG was 31 weeks. There was a range of indications for undergoing a cCTG assessment, the most common of which was reduced fetal movements which accounted for 26.6% (n=147) of cases. Other indications include abdominal pain in 20.1% (n=111) of cases, PV loss including suspected premature rupture of membranes, premature rupture of membranes and rupture of membranes in 16.8% (n=93) of cases, maternal medical complications (15.6% n= 86) and fetal abnormalities (9.9% n=55). We defined normal STV as ≥5.0bpms, which we based upon data from singleton pregnancies and clinical experience due to the lack of data on STV in twins, this was seen in both twins in 98.3% (n=550) of cases. In those with an abnormal STV only one twin was affected in 77.8% (n=7) of cases and both twins affected in 22.2% (n=2) of cases. 87.8% (n=491) of twins both met the DR Criteria with either only one or neither twins meeting this in 12.2% (n=68) of cases. In 3 cases (0.5%) the CTG assessment was an indication to expedite delivery. These results are displayed in table 15.

Table 15: *A table summarizing the characteristics of the CTGs recorded from the women in our cohort. (CTG: cardiotocography, PV: per vagina, STV: short term variation)*

Characteristic:	**Number:**
Number of CTGs per women:	2 (2)
Gestation at 1st CTG (weeks):	31 (6)
Indication for CTG:	
· *Reduced fetal movements:*	147 (26.6%)
· *Abdominal pain:*	111 (20.1%)
· *PV loss:*	93 (16.8%)
· *Maternal medical complications:*	86 (15.6%)
· *Fetal abnormalities:*	55 (9.9%)
· *Antepartum haemorrhage:*	20 (3.6%)
· *Other:*	40 (7.2%)
Short term variation: *(normal: STV ≥5.0 bpms)*	
· *Both twins normal:*	550 (98.3%)
· *One fetus abnormal:*	7 (1.3%)
· *Both twins abnormal:*	2 (0.4%)
Dawes Redman Criteria:	
· *Both twins met:*	491 (87.8%)
· *One twin met:*	50 (8.9%)
· *Neither twins met:*	18 (3.2%)
Time to meet criteria (minutes):	14 (10-60)
CTG indication to expedite delivery:	3 (0.5%)

Data are presented as n (SD) or n (%).

5.4.3 Neonatal outcomes

The neonatal outcomes of our study population are summarised in table 16. The mean gestational age of delivery was 36 with a range between 27 to 39 weeks gestation. There were two cases of still-birth (0.8%) both of which were in DCDA twins and affected one fetus in the twin pair. 48.6% (n=256) of the fetuses delivered were female with a median birth weight of 2380g. 5.3% (n=14) of neonates had an APGAR score <7 at 5 minutes, 3.6% (n=19) had a cord pH ≤7.10 and there were 246 admissions to NICU representing 46.6% of the fetuses. 19.1% of fetuses were affected by an adverse event including respiratory pathologies (18.0% n=95), new-born sepsis (1.7% n=9) and retinopathy of prematurity (0.4% n=2). There were two (0.4%) neonatal deaths.

***Table 16**: A table summarizing the neonatal outcomes of our cohort. (NICU: neonatal intensive care unit)*

Outcome	Number
Gestation at delivery:	36 (27-39)
· *Both twins live birth:* · *One fetus still birth:* · *Both fetuses still birth:*	262 (99.2%) 2 (0.8%) 0
Female sex:	256 (48.6%)
Birth weight (g):	2380 (1958- 2695)
APGAR Score <7 at 5 minutes:	14 (5.3%)
NICU Admission:	246 (46.6%)
Cord pH ≤7.10:	19 (3.6%)
Neonatal adverse events: · *Respiratory pathology:*	101 (19.1%) 95 (18.0%)

· *27-29 weeks gestation:*	9 (9.4%)
· *30-32 weeks gestation:*	51 (53.7%)
· *33-35 weeks gestation:*	15 (15.8%)
· *36-38 weeks gestation:*	20 (21.1%)
· *New-born sepsis:*	9 (1.7%)
· *27-29 weeks gestation:*	2 (22.3%)
· *30-32 weeks gestation:*	3 (33.3%)
· *33-35 weeks gestation:*	3 (33.3%)
· *36-38 weeks gestation:*	1 (11.1%)
· *Retinopathy of prematurity:* *Both cases at 30 weeks gestation*	2 (0.4%)
Neonatal deaths:	2 (0.4%)

Data are presented as n (IQR) or n (%)

5.5 Discussion

5.5.1 Findings

In this study we found that both fetuses had a normal STV and met the DR criteria in the majority of cases. However, in those with an abnormal STV or failure to meet DR criteria, intervention to expedite delivery was infrequent (6.5% n=3). Decreased STV and failure to meet the DR criteria can represent fetal distress, a complication requiring further medical management. The lack of subsequent intervention, particularly in cases of abnormal STV, raises two question; the ability of cCTG readings to accurately assess fetal wellbeing and detect cases of fetal compromise as well as the urgency for medical intervention when abnormal readings are produced. Additionally, we found 19 (3.6%) cases of cord pH <7.1, an indication of hypoxia close to and during delivery. Whilst we did not assess intrapartum cCTGs so cannot account for these, the number of abnormal STVs compared

to cases of fetal acidaemia do not match, questioning the reliability of cCTGs to detect fetal compromise in twins. However, it is important to note that in many cases the cCTG was recorded over 48 hours prior to delivery and so the ability for cCTG findings to predict and be correlated to neonatal outcomes is not possible.

Further, we found a high level of neonatal adverse outcomes and NICU admissions with 48.6% (n=256) of neonates in our study population admitted to NICU and 19.1% (101) experiencing adverse outcomes. However, 43.4% (n=115) of the pregnancies delivered at 35 weeks gestation or less so these outcomes can be somewhat attributed to the effects of prematurity. Nevertheless, the potential link between adverse neonatal outcomes and abnormal cCTG findings that have not triggered intervention should be investigated further.

Literature on the use of cCTGs in twin pregnancies is extremely limited, therefore we have been unable to compare our findings with existing studies and it is difficult to fully assess the reliability and reproducibility of our findings.

5.5.2 Strengths and Limitations

To our knowledge this is the first study evaluating the use of cCTGs to assess fetal wellbeing in twin pregnancies. Our retrospective cohort study provides insight into the frequency and gestation at which women pregnant with twins undergo cCTG monitoring as well as the indication for doing so. We have provided information on the proportion of fetuses with normal/abnormal STVs and those meeting or failing to meet the DR criteria. Subsequent information on neonatal outcomes offers some understanding of the ability of cCTGs to assess fetal wellbeing and improve neonatal outcomes.

A limitation of this study is the cohort size. With only 265 twin pregnancies it is difficult to make any definitive conclusions over the use of cCTGs as an assessment of fetal wellbeing and the link

between abnormal cCTG findings and adverse neonatal outcomes. In addition, the only measure of assessment in response to abnormal cCTG findings we measured was expedition of delivery. To assess whether cCTGs are considered reliable by healthcare professionals are promptly acted upon when abnormal, further measures of assessment such as senior obstetric review or ultrasound doppler assessment should be measured.

5.5.3 Future research

Despite providing interesting and useful initial insight into the use of cCTGs as an assessment of fetal wellbeing in twin pregnancies, further in-depth research into this area is required. Initially it would be useful to carry out a study comparing cCTG characteristics between singleton and twin pregnancies in order to validate the use of cCTGS in twins, ensuring that the correct parameters for normality are being used. Further to that, our study has demonstrated the need for a larger scale, multi-centre study that investigates the level of intervention in cases abnormal cCTG findings and whether intervention or non-intervention significantly improves neonatal outcomes. To properly assess this, prematurity and antenatal fetal complications should be accounted for and further analyses of intrapartum cCTGs should be assessed to investigate their role in detecting fetal acidaemia.

5.6 Conclusions

The use of cCTGs as an assessment of fetal wellbeing in twin pregnancies is an area in great need of research. We have demonstrated the frequency of and indications for antenatal cCTGs in twin pregnancies and highlighted the necessity for further investigation into the accuracy of cCTGs in detecting fetal distress as well as the threshold for intervention in cases of abnormal readings.

Chapter 6: Discussion

6.1 Aims addressed

The aim of this thesis was to identify predictors of intrapartum outcomes in multiple pregnancy as well as exploring various other aspects of management of twin pregnancies. This included reviewing current international guidelines on the management of multiple pregnancy to identify areas of consensus and conflict, systematically reviewing literature to assess the outcomes of induction of labour versus standard care in women pregnant with twins at term and observing the use of cCTGs in twin pregnancies to assess features that correlate to fetal wellbeing.

6.2 Key findings

We found that there was consensus in many aspects of international guidelines on the management of multiple pregnancy including determination of amnionicity and chorionicity within the first trimester, fetal anomaly scan between 18-22 weeks and recommended screening for TTTS. In the guidelines that provided intrapartum guidance there was consensus in recommending caesarean section to deliver MCMA twins, epidural anaesthesia for intrapartum analgesia and the use of CTG for intrapartum fetal monitoring. Overall, there was a distinct lack of guidance on intrapartum management.

Our systematic review found there was a lack of good quality studies assessing the outcomes of induction of labour versus standard care in twin pregnancies at term. Therefore, we were unable to identify any significant findings due to insufficient data. This demonstrated the need for a further large-scale randomised control trial in this area.

We identified multiparity, previous vaginal delivery, high Bishop's score and use of epidural anaesthesia to be predictors of successful vaginal delivery in twins, whilst a history of fertility treatment and non-cephalic presentation of either twin are associated with unsuccessful vaginal

delivery in twin pregnancies. We developed a high performing clinical prediction model that allows individual prediction of success of vaginal delivery for women pregnant with twins.

Our study observing the use of cCTGs in twin pregnancies demonstrated that women pregnant with twins have on average two antenatal cCTGs throughout pregnancy with the most likely indications being reduced fetal movements, abdominal pain or PV loss. We highlighted the need for further investigation into the accuracy of cCTGs in detecting fetal distress as well as an assessment of appropriate actions based on cCTG parameters in twin populations.

6.3 Implications for research

Throughout the writing of this thesis, gaps in current literature were identified. This, along with the findings we have demonstrated has highlighted key aspects of twin pregnancy management which are in need of further attention.

6.3.1 Review of international guidance on the management of multiple pregnancy

This review demonstrated the lack of intrapartum guidance for twin pregnancies, likely due to a lack of evidence in this area. In order to produce complete and comprehensive guidance further research into factors associated with improved intrapartum outcomes in twins is required. Particularly regarding the timing of delivery for DCDA twins, the timing and methods of induction of labour in twin pregnancies, management between the delivery of the leading and second twin and the mode of delivery if the second twin is non-cephalic.

6.3.2 Induction of labour between 37^{+0} and 40^{+6} weeks gestation – a systematic review of literature

Following our systematic review, we explained the need for a multi-centre, randomised control trial investigating the effects of induction of labour at 37^{+0} weeks gestation versus expectant management in order to address the lack of evidence in this area. The primary outcomes for this study would be intrapartum fetal deaths and early neonatal deaths with secondary outcomes expansively covering neonatal adverse outcomes. Data would be collected on antenatal maternal and fetal characteristics, outcomes of labour and delivery and neonatal outcomes. Findings from this trial would provide clarity as to the safest management plan for women pregnant with twins at term.

6.3.3 A retrospective cohort study assessing intrapartum outcomes in twin pregnancies at Liverpool Women's Hospital from 2010-2020

Our retrospective cohort study found that cases where twin 2 is non-cephalic are less likely to achieve successful vaginal delivery. This was not supported by previous literature that we identified, and has therefore demonstrated the need to investigate this factor further. An assimilation of all current data looking into the presentation of twin 2 and outcomes of delivery in the form of a systematic review and meta-analysis would hopefully produce a large enough overall cohort provide a conclusion to this question.

6.3.4 The use of Computerised Cardiotocography to assess fetal wellbeing in twin pregnancies

Through investigating the use of cCTGs in twin pregnancy as an assessment of fetal wellbeing we identified areas that require further research. Firstly, whether cCTGs can accurately identify cases of fetal distress in twin pregnancies. Secondly, whether abnormal cCTGs are appropriately acted upon by healthcare professionals and subsequently whether intervention in cases that are abnormal

improves neonatal outcomes. These questions could all be addressed in a multi-centre, large scale cohort study.

6.4 Implications for practice

Our review of international guidelines on the management of multiple pregnancy demonstrated the need for unified guidance. With current guidelines differing in various recommendations there is a high likelihood that maternal and fetal outcomes in twin deliveries vary around the globe, depending on which guidance is followed. Collaboration from leading institutions and professionals internationally is needed in order to ensure that where possible, each woman and her fetuses receive the care that will give them the best possible outcomes.

The clinical prediction model to predict successful vaginal delivery in twins that we have developed from our retrospective cohort study has potential to be used in daily in clinical practice. With further assessments to ensure accuracy and reliability, the model could be translated into an app or website to be used by obstetricians. This would allow these doctors to counsel individual patients, visually demonstrating the chance they have of a successful vaginal delivery, allowing informed decision making involving both the patient and healthcare professionals.

The recent 2022 Ockenden report (141), reviewing the maternity services at Shrewsbury and Telford Hospital NHS Trust demonstrated the national need for improved care and safety throughout maternity services. One of the many measures introduced as a result of this report is improving the care of women with complex pregnancies, including multiple pregnancy. This involves management by a dedicated consultant and specialist midwife as well as ensuring each woman has a robust plan of care, developed collaboratively with both the clinicians and the woman. Aspects of this thesis have highlighted the importance of involving women in the conversations surrounding their care and management options as well as providing them with adequate information so that they can make

informed decisions. Appropriate use of the clinical prediction tool we have developed and application of the findings of this thesis can further aid these conversations, helping women to have autonomy and improving the care that is given throughout multiple pregnancy services.

6.5 Final conclusions

Our guideline and literature reviews have demonstrated the paucity of evidence on the management of delivery of twin pregnancies. Our retrospective cohort study in which over two thirds of women achieved a vaginal delivery of both twins has shown that women pregnant with twins who are multiparous, have had a previous vaginal delivery, a high Bishop's score and use epidural anaesthesia are more likely to have a successful vaginal delivery of both twins. Conversely, women who have a history of fertility treatment or non-cephalic presentation of either twin are less likely to achieve this. This information provides clarity lacking in current literature and can aid clinical decisions made by healthcare professionals caring for women pregnant with twins. The use of our clinical prediction model has good potential for use in obstetrics care, particularly if it's accuracy, validity and reliability can be validated in other populations. Future studies are required to investigate the safest management strategy for women pregnant with twins at term, as well as an assessment of the reliability of cCTGs to detect fetal distress and indicate triggers for intervention.

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