Twin pregnancy

Elizabeth Bonney
Medha Rathod
Kelly Cohen
Emma Ferriman

Abstract
Twin pregnancies account for 2–3% of all births. They carry significant risks to both mothers and babies. These risks include preterm delivery, intrauterine growth restriction and pre-eclampsia. In addition, monochorionic gestations confer an even higher rate of perinatal morbidity and mortality arising from a shared placenta due to placental anastomoses, which may lead to twin to twin transfusion syndrome (TTTS). It is essential that chorionicity is established in the first trimester in order to initiate the appropriate antenatal management and surveillance. In view of the high risk of both maternal and fetal complications, twin pregnancies are ideally managed in a dedicated clinic according to agreed protocols.

Keywords chorionicity; dichorionic; monochorionic; twins

Introduction
Twin pregnancies account for approximately 3% of all live births, but account for up to 15% of the overall perinatal mortality (Table 1). Monozygotic twin frequency rates remain relatively stable worldwide at 3–5/1000 pregnancies, but dizygotic twins have a varied rate depending on a number of factors including geographical location, assisted reproductive techniques and increasing maternal age. Rates vary from 1.3 to 49/1000 pregnancies. Monochorionic twin gestations are associated with even higher perinatal risk. Multiple pregnancies have been described as a modern epidemic and carry considerable resource implications for health providers. In order to reduce the numbers of twin pregnancies conceived as a result of assisted conception techniques, a number of strategies have been proposed such as elective single embryo transfer, selective fetal reduction and single blastocyst transfer.

Zygosity and chorionicity
Twin pregnancy usually results from the fertilization of more than one oocyte, producing dizygotic or non-identical fetuses. Splitting of a single fertilized oocyte produces a monozygotic twin pregnancy with two genetically-identical co-twins. Non-identical twins develop their own placentae: monozygous twins may share a placenta according to the time of separation (Figure 1). Dichorionicity occurs in 80% of twins, and genotyping is required to confirm zygosity in these cases.

Monozygotic twins share a single placenta and have a higher perinatal risk due to complications arising from a shared placenta. Risks include preterm delivery, intrauterine growth restriction and pre-eclampsia. In addition, monochorionic gestations are associated with an even higher rate of perinatal morbidity and mortality arising from a shared placenta due to placental anastomoses, which may lead to twin to twin transfusion syndrome (TTTS). It is essential that chorionicity is established in the first trimester in order to initiate appropriate antenatal management and surveillance. In view of the high risk of both maternal and fetal complications, twin pregnancies are ideally managed in a dedicated clinic according to agreed protocols.

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Introduction
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First trimester screening
The risk of Down’s syndrome is 1 in 800 pregnancies. The risk for monozygotic twins is the same as for singletons, but for dizygotic twins this risk is doubled as each twin has its own risk. Biochemical screening alone is not recommended in multiple gestations. The screening test of choice is nuchal translucency measurement, which has a detection rate of 85% when assessed between 11 and 13 + 6 weeks. The presence of a nasal bone and ductus venosus can also be assessed at this time, and assessment of tricuspid Dopplers performed. Combination with first trimester biochemistry (pregnancy associated plasma protein A (PAPP-A), human chorionic gonadotropin (HCG), alphafetoprotein (AFP) and oestriol can increase the detection rate further (up to 95%).

Following detection of an increased nuchal translucency, the option of invasive testing should be discussed. Both amniocentesis and CVS are possible in twin pregnancy, but these procedures should be performed in a specialist Fetal Medicine unit. The rates of miscarriage associated with invasive testing are quoted as 3–4% for CVS and 2.5% for amniocentesis.

Anomaly screening
The frequency of fetal abnormality in dizygotic twins is comparable to that of singleton pregnancies (2–3%). It contrasts with the increased frequency of anomalies seen in monozygotic pregnancies where rates of up to 10% have been reported, i.e 2–3 times
that which occurs in dizygotic twinning. Several different types of anomaly are thought to be more commonly seen in twin pregnancies including neural tube defects and congenital heart disease. In monozygotic twinning, abnormal vascular connections predispose to limb reduction defects and bowel atresias.

Disorders of laterality occur when embryonic migration has begun prior to zygotic splitting and may explain the increased incidence of cardiac anomalies in monozygotic twin pregnancies, where fetal echocardiogram assessment is ideally offered at 22–24 weeks.

While the majority of monozygotic twins appear to be almost identical, there are monozygotic offspring who are genetically and phenotypically dissimilar. Mechanisms may include unequal allocation of blastomeres between the two embryos, disrupted embryonic migration, somatic mosaicism or chimaerism, and variations in penetrance producing phenotypic discrepancy.

The type of discordance varies from genetic and chromosomal abnormalities through to isolated structural anomalies. Discordant single gene disorders, imprinting defects and aneuploidy have all been reported in monozygotic twins. Case reports detail a range of discordant structural anomalies found in monozygotic twin pairs, from neural tube defects and holoprosencephaly to lateral and ventral body wall defects, and anomalies related to the VATER association.

Management of twins discordant for fetal anomaly

The diagnosis of discordant anomaly in twins creates significant dilemmas for parents, and careful counselling is required in centres with expertise in this area. Accurate diagnosis and determination of chorionicity is critical for subsequent management. Depending on the anomaly detected, parents may be faced with a choice of continuing the pregnancy and delivering both a normal and an affected baby, or of terminating the affected fetus and risking the viability of the healthy co-twin. Invasive testing for chromosomal abnormality in dichorionic twins requires dual puncture in most cases. In general, monochorionic twins require a single puncture but in cases of discordant anomaly then both fetuses should be sampled.

Selective feticide of the affected fetus is only possible in dichorionic twin pairs due to their separate inter-twin circulations. It is associated with an increased risk of pregnancy loss, and if not performed in the first trimester is usually delayed until the third trimester when viability of the normal twin is more certain. This must be balanced against the risk of spontaneous premature labour, especially in cases complicated by polyhydramnios such as anencephaly.

Abnormalities specific to twins

Complications specific to both mono- and dichorionic twin pregnancies include vanishing twin and fetus papyraceous. Abnormalities unique to monochorionic pregnancies only are the twin-to-twin transfusion syndrome (TTTS) and the twin reversed arterial perfusion sequence (TRAP). Monoamniotic pregnancies will also be discussed.

Vanishing twin and fetus papyraceous

Up to 21% of twin pregnancies are said to be complicated by either miscarriage or loss of one twin in the early stages. This
‘vanishing twin’ phenomena is increasingly detected since the advent of high resolution ultrasound, and it is suggested that the miscarriage rate in these pregnancies is about five times higher than that of normal twins. No increased monitoring should be necessary if the baby appears structurally normal, as the pregnancy is most likely to progress as expected for a singleton fetus.

Loss of a co-twin in the second or third trimester carries a risk of preterm delivery, neurological sequelae or death to the remaining fetus. It may result in the phenomenon known as fetus papyraceous, where the anatomically-preserved demise fetus can be identified at the later delivery of the surviving twin.

**Anomalies confined to monochorionic gestations**

**Twin to twin transfusion syndrome (TTTS)**

Twin-to-twin transfusion syndrome (TTTS) complicates 10–20% of monochorionic twin pregnancies. Feto-fetal transfusion occurs via multiple vascular anastomoses between the circulations of each co-twin, such that there is a net flow of blood from one twin (the ‘donor’) to the other (the ‘recipient’). This results in hypervolaemia and oligohydramnios in the donor twin and hypovolaemia and polyhydramnios in the recipient.

Progression of the syndrome in the donor leads to growth restriction and in severe cases, absent or reversed end-diastolic frequencies in the umbilical artery. The recipient may develop organomegaly, with abnormal ductus venosus Doppler frequencies related to polycythaemia and hydrops. Tricuspid regurgitation is an ominous sign of cardiac dysfunction in the recipient and is associated with significant postnatal cardiac dysfunction (Figure 2).

**Pathophysiology:** both superficial and deep placental vascular connections are present in the monochorionic placenta. Deep anastomoses occur between arteries and veins. These arteriovenous (AV) connections are unidirectional, and require the presence of ‘balancing’ superficial anastomoses to prevent TTTS. Superficial anastomoses are bi-directional and are commonly found between arteries (arterio-arterial anastomoses) and veins (veno-venous anastomoses). Bidirectional flow allows compensatory activity in the event of pressure differences within the placenta, and if reduced or absent this predisposes to TTTS.

**Diagnosis of TTTS:** most commonly, the diagnosis of TTTS is made in the second trimester following the detection of discordant growth or discrepant liquor volumes. A ‘stuck twin’ may be visible, compressed against the uterine wall, where the donor is constricted by anhydramnios and the tense sac of the polyhydramniotic co-twin. A discrepancy in nuchal translucency measurement in the first trimester is said to also be an early marker for TTTS. Acute TTTS may present as sudden onset maternal discomfort and increasing girth, following rapid development of polyhydramnios. Mortality is extremely high usually as a consequence of premature delivery, either spontaneous or iatrogenic.

A diagnostic staging system proposed by Quintero describes a progression from early (stage I) to late (stage IV) disease (Table 2). High stage at diagnosis is associated with increased neurological morbidity and mortality, but progression of disease from early to more advanced stage is also important for prognosis. Uncertainty exists regarding the optimum management of early (stage I) disease, where there is some evidence that aggressive treatment may confer little benefit.

**Management options:** Several management options exist for the treatment of TTTS, including laser ablation of the communicating placental vessels, serial amnioreduction with or without septostomy, and occlusive feticide. It may be appropriate to consider conservative or expectant management, or to offer a termination of pregnancy if the fetuses are extremely premature or severely compromised.

**Laser ablation** — endoscopic placental laser ablation aims to coagulate the vascular anastomoses contributing to TTTS. Endoscopic placental laser ablation aims to coagulate the vascular anastomoses contributing to TTTS, and may be selective or non-selective. Non-selective coagulation destroys all vessels crossing the intertwin membrane, including the healthy circulation, and may increase mortality in the donor twin. This method has been largely superseded by selective ablation, which ablates...
only specific connections. Amnioreduction is performed following laser ablation in most cases.

The Eurofetus randomized trial demonstrated increased survival of one or both twins following laser (76%) compared with serial amnioreduction (56%). Median gestational age at delivery was increased in the laser group (33 weeks vs 29 weeks) and laser was associated with a reduced incidence of periventricular leukomalacia. As live birth rates were similar in both groups, this survival advantage may reflect the differences in gestation rather than a consequence of the therapy. In addition, early stage disease was not well-represented in this study, leaving persistent doubt about the benefit of laser in early disease.

A systematic Cochrane review in 2008 included only two randomized controlled trials (including Eurofetus) with similar results. Long term, neurological sequelae have a reported incidence of 13%—17% and do not appear to be reduced following laser compared with amniotrainage.

Following successful laser ablation, the incidence of intrauterine death is reported to be 13–33%, and that of ruptured membranes approaching 10%. High stage disease is more likely to result in mortality. Late complications of laser are increasingly reported, and mainly relate to the presence of persistent communicating vessels causing recurrent TTTS or reversal of flow (reverse TTTS). Despite this, since the Eurofetus study, laser has been considered the first-line treatment for TTTS.

**Serial amnioreduction and septostomy** — amnioreduction aims to reduce liquor volume in the recipient twin and to prevent premature delivery. It is likely to require repeated procedures and does not treat the underlying cause of feto-fetal transfusion. Associated risks include premature labour, ruptured membranes, choioamnionitis and placental abruption. Septostomy aims to disrupt the inter-twin membrane allowing normalisation of liquor volume between the two sacs, and may be followed by amniodrainage as an adjunctive treatment.

A randomized controlled trial comparing amnioreduction with septostomy in TTTS before 24 weeks of gestation found that the rate of survival of at least one twin was similar in both groups (78% vs 80%), with no significant advantage of septostomy over amnioreduction alone.

Possible disadvantages of septostomy include the fact that the resulting chorioamniotic separation may hinder subsequent laser ablation. Amnioreduction is now most commonly utilized at later gestations or where laser ablation is not feasible, and is useful in stage I disease where the evidence for laser ablation is less robust.

**Selective occlusion** — the termination of one fetus by cord occlusion is an option particularly in the presence of discordant anomaly. Parents may choose to terminate a severely affected twin to increase survival chances in the other, less affected twin and reduce the risk of losing both babies. Single survival rates in the limited evidence available would appear to be similar to single survival rates achievable by laser ablation.

**Twin reversed arterial perfusion sequence (TRAP)**

Acardiac anomaly is a rare complication of monochorionic twin pregnancies, occurring in approximately 1 in 35 000 cases. In this condition, arterial blood flows in a retrograde fashion from the pump twin towards the affected twin via a single arterio-arterial anastomosis, hence the synonym twin reversed arterial perfusion syndrome (TRAP). The poorly-oxygenated blood entering the circulation of the affected twin preferentially perfuses the caudal structures rather than the cephalad, resulting in abnormal development of all organ systems. The head and the heart are commonly absent, with a preserved central trunk and rudimentary spine. Lower limbs may be more preserved due to the improved blood supply. Acardiac twins are frequently hydropic due to their abnormal lymphatic and vascular drainage.

The diagnosis of TRAP usually follows the detection of a grossly abnormal co-twin within a monochorionic pair. The absence of cardiac pulsation in the acardiac twin is usually evident, although rudimentary cardiac tissue or transmitted pulsations may produce appearances of normal cardiac function. Paradoxical blood flow may be visualized by colour Doppler ultrasound to confirm the diagnosis.

Once diagnosed, the primary aim of management is to improve survival chances for the structurally normal pump twin. Poor prognostic features include increasing size of the acardiac twin, with signs of cardiac insufficiency in the donor secondary to increased demand. Management options for intervention include cord occlusion techniques, or an intrafetal approach to ablate the vasculature in the acardiac twin.

**Monochorionic, monoamniotic twins**

Monoamniotic twinning occurs in 1—2 % of monochorionic gestations (1 in 3000—6000 pregnancies) and occurs as a result of zygotic separation beyond eight days of conception. Diagnosis is usually following first trimester ultrasound, showing a single placenta and two freely-moving fetuses with no inter-twin membrane evident.

These pregnancies are associated with the highest perinatal loss rate of all twin forms, at around 30—60% in most series. Umbilical cord accidents and prematurity account for much of this loss rate, along with higher rates of congenital anomaly (20—25%) and growth restriction. More recent series suggest a fall in perinatal mortality, possibly associated with earlier diagnosis and intensive surveillance in these cases. Despite the shared placenta chronic TTTS appears less common in these gestations (5%).

Up to 60% of the antenatal fetal deaths occur prior to 32 weeks’ gestation. This is thought to be related to cord entanglement and occlusion, although cord entanglement will be present in almost all gestations. Consequently this complication is not preventable and cannot be predicted by cardiotocographic monitoring. Strategies have been reported to reduce amniotic fluid levels, limiting fetal movement to prevent tightening of the tangled cords. Medical amnioreduction with oral prostaglandin synthase inhibitors has been described with 100% survival of forty fetuses (twenty pairs). However, the majority of monoamniotic pregnancies undergo intensive surveillance with CTG monitoring and serial ultrasound in an attempt to detect impending cord occlusion.

Elective delivery at 32 weeks’ gestation following administration of steroids is usually advocated, since at this point neonatal survival is comparable to term survival in most centres. Meta-analyses of perinatal loss report a rate of around 10% in monoamniotic pregnancies continuing beyond this point. Vaginal delivery of monoamniotic pairs has been achieved successfully, but is associated with risks of cord prolapse and fetal impaction in the maternal pelvis. Vaginal delivery is usually reserved for the extremely premature or non-viable fetuses.
Conjoined twins

Incomplete division of the embryo may result in conjoined twins. Classification of this anomaly is largely descriptive and dependent on the anatomical areas joined. Conjoined thorax (thoracopagus) and conjoined thorax and abdomen (thoraco-omphalopagus) are the commonest subtypes with pelvis and head (ischiopagus and craniopagus) being less common.

With the advent of improved ultrasound techniques, most cases are identified in the first trimester, and in view of the significant mortality and morbidity a significant number of parents will opt for termination. Survival depends on the organs joined. 50% are stillborn and of the survivors up to 75% may have inoperable defects. Elective delivery is usually advocated, but there are reports of vaginal deliveries occurring.

Antenatal management

Women with twin pregnancies should be given the same advice about diet, lifestyle and nutritional supplements as in routine standard care. There is a higher incidence of anaemia in women with twin pregnancies therefore a full blood count should be performed at 20—24 weeks to identify women who need supplementation of iron or folic acid. This should then be repeated at 28 weeks as in routine antenatal care.

It is vital to offer antenatal care in an appropriate setting aiming to provide standardized care to all women with multiple pregnancies. Clinical care for women with twin pregnancies should be provided by a nominated multidisciplinary team consisting of named specialist obstetricians, specialist midwives and ultrasonographers, all of whom have experience and knowledge of managing twin pregnancies. A dedicated clinic allows the close surveillance required by this population along with the specialized care they may need in terms of preparation for birth and psychological support. Mothers with twin pregnancies are at higher risk of all obstetric complications and should be counselled appropriately (Table 3). In general, maternal mortality associated with multiple births is 2.5 times higher than singleton births.

NICE and the RCOG consensus document has recommended two distinct care pathways for monochorionic and dichorionic twins (Table 4).

Hypertension

Women with twin pregnancies may be at higher risk of hypertension. NICE suggest women with multiple pregnancies should take 75 mg of aspirin daily from 12 weeks until the birth of their babies if they have one or more of the following risk factors for hypertension:

- First pregnancy
- Age 40 years or older
- Pregnancy interval of more than 10 years
- BMI of 35 kg/m² or more at first visit
- Family history of pre-eclampsia.

Preterm birth

Twin pregnancies are at higher risk of spontaneous or iatrogenic preterm delivery. The incidence of preterm delivery prior to 37 weeks can be up to 60 %. Delivery at less than 32 weeks appears to vary with the type of twinning, ranging from 5% for DC and 10% for MC twins compared with 1% for singleton pregnancies. Recent evidence suggests that progesterone supplementation does not prevent early preterm labour in twin pregnancies and the use of untargeted single or multiple courses of corticosteroids is not recommended.

Intrauterine growth restriction

Twin pregnancies are known to be at a significantly increased risk of intrauterine growth restriction, with rates varying from 20% in dichorionic twins to 30% in monochorionic pairs. It is important to estimate fetal weight discordance using two or more biometric parameters at each ultrasound scan from 20 weeks. Consider a 25% or greater difference in size between twins as a clinically important indicator of growth restriction and offer referral to a tertiary level fetal medicine centre.

Pregnancy outcome is determined by the severity of the growth restriction and by the gestation at diagnosis. Growth in dichorionic pregnancies reflects both genetic potential and placental function, but monochorionic twin growth is also

### Antenatal management of twin pregnancies

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<th>Scans</th>
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<th>MCDA</th>
<th>MCMA</th>
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<td>11 + 0 to 13</td>
<td>NT ± serum</td>
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<td>+ 6 weeks</td>
<td>Chorionicity Viability</td>
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<td>16, 18 weeks</td>
<td>Ftortnightly surveillance for TTTS</td>
<td>Anomaly Fetal echocardiogram Surveillance for TTTS</td>
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<td>20 weeks</td>
<td>Anomaly</td>
<td>Fetal echocardiogram Surveillance for TTTS</td>
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<td>22 weeks</td>
<td>Growth</td>
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<td>24, 28, 32</td>
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<td>weeks</td>
<td>34</td>
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<td>Delivery</td>
<td>37—38 weeks</td>
<td>36—37 weeks after corticosteroids</td>
<td>32 weeks after corticosteroids</td>
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Table 4

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<th>Maternal risks associated with multiple pregnancy</th>
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<td>Hyperemesis</td>
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<td>Increased mechanical symptoms of pregnancy</td>
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<td>Anaemia</td>
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<td>Operative delivery</td>
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<td>Post-partum haemorrhage</td>
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<td>Perinatal mental health disorders</td>
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Table 3
subject to the effects of unequal blastomere separation and placental vascular communications. Early-onset discordant growth restriction may be detected by large inter-twin disparities between crown-rump lengths, and should be referred to a tertiary centre for fetal medicine opinion. In monochorionic twins where the co-twin is at risk, selective cord occlusion may be an option in severely discrepant pairs.

The optimum surveillance for IUGR in twins less than 32 weeks with abnormal Doppler studies has not been defined. The timing of delivery at very early gestations is a balance of risks of prematurity and risk of exposing the fetus to prolonged hypoxaemia. Surveillance of growth-restricted twins will include monitoring of fetal Dopplers (umbilical artery, MCA and ductus venosus), liquor volume and biophysical profile.

**Single intrauterine fetal death**

The death of one twin carries an increased risk to the remaining fetus which is greater in monochorionic pregnancies. The surviving twin of a monochorionic pair has a 12% risk of death, with neurological sequelae in 18% and preterm delivery in 68%. In dichorionic pairs the risk of death is just 1%, with 4% developing neurological disability and under 50% subsequently delivering prematurely. This significant difference in risk has been attributed to massive haemodynamic shifts within the shared placenta following the death of one fetus. These patients should be carefully counselled regarding the prognosis for the surviving twin, and MRI of the fetal brain is advocated in monochorionic gestations.

**Delivery**

NICE guidance recommends delivery at 37–38 weeks for dichorionic twins and 36–37 weeks for monochorionic diamniotic twins, but marked variability in policy exists in practice. There is growing evidence that perinatal mortality rates increase after 38 weeks even in uncomplicated twin pregnancies. Additionally, intervention at 37 weeks does not appear to be associated with a significant difference in mode of delivery or maternal complications when compared to expectant management.

Retrospective cohort data suggests that, when compared to the presenting twin, the second twin is at higher risk of intrapartum mortality due to the complications of vaginal delivery. This large randomized, controlled trial compares planned Caesarean section to planned vaginal birth for twins between 32 and 38 weeks’ gestation, and is powered to detect a halving of perinatal mortality or serious morbidity with a policy of planned Caesarean section. Preliminary results from the Twin Birth study suggest there is no advantage to a policy of planned caesarean section for twins with respect to both maternal and neonatal morbidity. Current practice supports the policy of planned vaginal birth in uncomplicated pregnancies with a cephalic first twin, unless the mother prefers Caesarean delivery.

On a more practical level, delivery should be conducted in a unit where continuous electronic fetal monitoring is available and where there is access to early recourse to Caesarean section. An experienced operator should be present at delivery to enable expert management of the second twin in particular with regard to vaginal breech delivery. Overall, there is a higher risk of a Caesarean section for twin pregnancies (Caesarean section rates in our institution, a large teaching hospital in Northern England, UK, are 47% overall and 1% for the second twin).

**Conclusions**

Multiple pregnancy is a common cause of morbidity for both mothers and babies. Antenatal care focuses on screening for both anomalies and for early signs of complications such as growth restriction and TTTS. Accurate diagnosis of chorionicity in the first trimester is essential, and allows appropriate surveillance to be planned. Uncertainty regarding the optimum mode and timing of delivery for twin pregnancies still exists in the absence of robust controlled trials. Currently, most units in the UK would support a practice of planned vaginal delivery in uncomplicated twin pregnancies.

**FURTHER READING**


**Practice points**

- Early assessment of chorionicity is critical for planning subsequent management.
- Referral for appropriate first trimester screening (nuchal translucency and first trimester biochemistry), and invasive procedures in twin pregnancies should be performed in a fetal medicine unit.
- Clinicians should appreciate the increased risk of congenital anomaly, in particular congenital heart defects in monochorionic twins.
- Discordant fetal growth should be referred to a specialist centre when diagnosed.
- The appropriate antenatal pathways should be followed with increased surveillance of monochorionic twins.
- In twins planning a vaginal delivery, an experienced practitioner must be present or easily accessible during the intrapartum period.