Twin pregnancy: the role of ultrasound in management

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Determination of chorionicity is one of the most important issues in the management of twin pregnancy. Modern ultrasound equipment has made it possible to accurately assess placentation already in the first trimester with the lambda sign. With regard to prenatal diagnosis, it is important to know the chorionicity in order to calculate the risk of chromosomally abnormal fetuses. Accurate chorionicity offers the obstetricians the opportunity to observe the monochorionic twins more intensively than is required for twins with dichorionic placentation. This review gives an update of the state of the art for clinicians caring for twin pregnancies.

Key words: abortion; amniocentesis; amnion; amnion fluid; brain damage; biochemical screening; cervix uteri; chorion; chorionic villi sampling; chromosome abnormalities; endoscopy; fetal death; fetal growth; fetofetal transfusion; genetic counseling; malformations; multiple pregnancy; placentation; prenatal; prenatal diagnosis; preterm delivery; twin pregnancy; ultrasonography

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The incidence of multiple gestations is increasing, primarily because of delayed childbearing and the use of assisted reproductive technologies. Twin pregnancies have a higher incidence of complications than singletons, from the first trimester until the delivery of the second fetus. Ultrasonographic evaluation throughout all three trimesters has allowed a closer and more differentiated monitoring of twin pregnancies.

This paper gives an overview of the management of twin pregnancies with special emphasis on the role of ultrasonography.

Abbreviations:
AC: amniocentesis; CVS: chorionic villus sampling; DC: dichorionic; DZ: dizygotic; DS: Down’s syndrome; IUGR: intrauterine growth retardation; MC: monochorionic; MZ: monozygotic; NT: nuchal translucency; SGA: small for gestational age; TTTS: twin-twin transfusion syndrome.

Biology
Zygocity, chorionicity and amnionicity

There are two major types of twin gestations: dizygotic (DZ) and monozygotic (MZ). MZ twins occur sporadically, while the incidence of DZ twins increases with advancing age, parity and with ovulation induction. The higher rate of DZ twins observed with advancing maternal age may be caused by an elevation of gonadotrophin levels with age (1). In some families DZ twinning is apparently inherited (2). The twinning frequency is 2–45/1 000 deliveries, with a considerable variation between countries. This variation is largely caused by differences in the occurrence of DZ twins, while that of MZ twins is similar throughout the world. In Caucasians about 30% of twin pregnancies are MZ and about 70% DZ.

Zygocity refers to the type of conception: MZ twins result from the splitting of one fertilized
ovum during the first two weeks of embryogenesis, whereas DZ twins are due to the fertilization of two ova by different spermatozoa (2, 3).

Chorionicity denotes the type of placentation. Twin placetas are classified into two categories according to the number of layers in the septum between the two amniotic sacs. In the monochorionic (MC) placenta the septum consists of two layers of amnion, while in the dichorionic (DC) placenta it has two layers of both chorion and amnion. DC placetas may be fused or separate, but when examined after delivery blood vessel anastomoses between the two placental vascular beds are seldom found (4).

If two distinct placetas are identified, the pregnancy is DC. In the case of a single placenta, however, the pregnancy may be MC or DC. Chorionicity may be determined by looking for the ‘twin peak sign’ (5) or ‘lambda sign’ (6, 7), which is only seen in DC pregnancies. This sign reflects the persistence of the chorion frondosum, which is seen as a triangular projection extending between the two layers of amniotic membrane. This sign accurately identifies chorionicity in 99–100% of twins between weeks 10 and 14 (8). As pregnancy progresses, the twin-peak sign becomes more difficult to visualize and indeed it has disappeared in about 7% of DC pregnancies at 16–20 weeks. Absence of the twin-peak sign in the second or third trimester can therefore not exclude dichorionicity (9, 10).

DZ twins are always DC and MC twins are always MZ. Depending on at which stage of the embryogenesis the zygote splits, four different types of twins may result (Fig. 1). DC diamniotic MZ twins result from the division of the zygote at the two-cell and morula stages (less than four days after fertilization) and represent about 26–28% of MZ twins. The division of the inner cell mass at four to eight days after fertilization causes MC diamniotic MZ twins, the most common type (70%). MC monoamniotic twins occur when the division takes place more than eight days after the fertilization and represent only 2–4% of the MZ twins. Incomplete division of the embryonic disk after 13 days causes conjoined twins.

Amnionicity in MC pregnancies can accurately be determined around 8 weeks of gestation, from which time it is possible to visualize the amniotic membrane. Earlier in the first trimester, the number of yolk sacs may be used to diagnose amnionicity. When two yolk sacs are seen in the extraembryonal celoma, the pregnancy will be diamniotic, while a single yolk sac will in most cases lead to monoamniotic twins and should prompt a follow up scan at 9–10 weeks to assign amnionicity definitively (11).

**Congenital anomalies**

Most studies of congenital anomalies in twins have not related their incidence to zygocity or placentation. Myrianthopoulos (12) and Baldwin (13) have both found that congenital anomalies were 1.2–2 times more common in twins than singletons. In DZ twins the rate per fetus is the same as in singletons, whereas in MZ twins the rate is 2–3 times higher. The most common structural abnormalities are cardiac, neural tube and brain defects, facial clefts, gastrointestinal, and anterior abdominal wall defect (14, 15). Among cardiac defects, especially persistent ductus arteriosus, single ventricle and ventricular septal defect are seen more often in twins (16, 17).

In a recent international registry study 5572 malformations were diagnosed in 260,865 twins, giving a 1.25 relative risk (95% confidence interval 1.21–1.28) of congenital anomalies in twins compared to singletons from the same registries (17). This study confirmed that the anomalies mentioned above are significantly more common in twins, but also suggested that all anatomical systems appear to be involved (14, 15). The limitation of the study was that the incidence of malformations was neither correlated to chorionicity or zygocity, nor to the children’s sex.

For any given defect the pregnancy may be concordant or discordant in terms of both the type of abnormality and its severity. The majority of structural defects are discordant regardless of zygocity. Discordance in DC twins is usually due to differences in genetic predisposition, whereas in MC twins discordance may be a consequence of the underlying stimulus to zygote splitting, variation in gene expression, or a consequence of abnormal placentation (18). Apart from the struc-

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![Figure 1](image-url)  
*Fig. 1. Four different types of twins.*
tural fetal defects, which also occur in singletons, there are three types of congenital anomalies unique to twin pregnancies. The first are midline structural defects believed to be a consequence of the twinning process, represented by conjoined twins. The second are malformations resulting from vascular anastomoses with the acardiac monster being the classical example. Malformations such as microcephaly, periventricular leukomalacia, hydrocephalus, intestinal atresia, renal dysplasia and limb amputation may also be secondary to vascular defects caused by the demise of a cotwin with subsequent hypotension, vascular thrombosis and/or ischemia in the surviving fetus. Thirdly, some defects or deformations may result from intrauterine crowding including foot deformities, dislocation of the hip and skull asymmetry (19). While the third group can be seen in MZ as well as DZ twins, the first two groups are unique to MZ twins. The congenital malformations unique to twin pregnancies are very rare.

Conjoined twins may be diagnosed by prenatal ultrasonography from 12 weeks of gestation. If the parents consider continuing the pregnancy, it is essential to perform a detailed ultrasound scan to assess which viscera are shared. Particular emphasis should be put on the examination of the fetal heart, as the prognosis for twins with a shared heart is very poor.

Risk of chromosome abnormalities in twin gestations

Because most twins are DZ and most trisomies result from non-disjunction during meiosis, before formation of the zygote, it may be assumed that each twin has an a priori risk of having an aneuploid chromosome complement. This assumes a probability of non-disjunction in the second twin independent of the chromosome complement of the first twin. In DZ twins, therefore, a chromosome abnormality will most likely involve only one of the twins. On the other hand, in MZ twins a chromosome abnormality will nearly always involve both twins. In very rare instances MZ twins may have different karyotypes, presumably as a result of postzygotic nondisjunction. On the basis of existing tables of estimated risks of chromosome abnormalities in singleton gestations (20), Rodis et al. (21) derived tables defining the age-related risks of chromosomal abnormalities in twin gestations. The expected risk of having at least one twin affected by Down’s syndrome (DS) was greater than that for a singleton of comparable maternal age. Indeed for a patient at 32 years of age with a twin gestation, the risk of having at least one twin affected by DS was similar to that of a 35-year old woman with a singleton gestation. However, the observed birth prevalence in 106 twin pregnancies with DS was only 3% greater than for singletons (22). A very high miscarriage rate in twins affected by DS could explain the discrepancy between the expected and the observed rates of Down’s syndrome (22).

Prenatal screening and diagnostic tests

Crown-rump length measurement

A difference in crown-rump length measurement between the two embryos may be the first sign of chromosome abnormality, major congenital anomalies or imminent demise in the smaller twin (23, 24). At less than eight weeks of gestation a difference of more than three mm was associated with a 50% risk of intra-uterine death of the smaller twin (25).

The consequences of intertwin disparity in crown-rump length were examined in a study of 123 MC and 416 DC twins (26). There was no correlation between intertwin disparity in crown-rump length and intertwin disparity in birth weight. In DC pregnancies a significantly higher intertwin disparity was found in those pregnancies with chromosomal abnormality, miscarriage or intruterine death in one or both fetuses as compared to those pregnancies resulting in two live births. This was not the case among the MC twin pregnancies. Previous smaller studies have shown the same results (23–25). An explanation could be that in DC pregnancy early-onset growth restriction due to a genetic defect or to impaired placentation occurs in one of the fetuses. In MC pregnancies, on the other hand, the genetic constitution and trophoblast invasion should be the same for the two fetuses and there does not seem to be a significant imbalance in the blood flow through the placental vascular communications at this stage of pregnancy (26). To determine the gestational age in twins, the largest CRL should be used.

Screening for trisomy 21 in twin pregnancies

Genetic counseling and prenatal diagnostic testing in twin gestation is complicated, because the methods of screening are less effective and the techniques of invasive testing may provide uncertain results or may be associated with higher risks of miscarriage. In addition, the fetuses may be discordant for an abnormality, in which case one of the options for the subsequent management of the pregnancy is selective feticide.
Biochemical screening

In singleton pregnancies screening by alfa-feto-protein (AFP), human chorionic gonadotropin (HCG) and unconjugated estriol in the second trimester yields a 70% detection rate for a 5% false-positive rate. In cases of twins, the underlying assumption is that each fetus contributes 50% of the analyzed level in maternal serum, but precise biochemical information about each co-twin is lacking. As most twin pregnancies are DZ and most likely have only one affected fetus, the presence of an unaffected co-twin will tend to bring the distributions for affected and unaffected twin pregnancies relatively closer together compared with affected and unaffected singleton pregnancies.

In the second trimester the median level of biochemical markers in unaffected twin pregnancies is about double that in singletons (27) with perhaps levels of unconjugated estriol being only 1.7 times that in singletons. The reported number of twins where one or both fetuses had DS is too small to calculate the marker distributions in affected twins. Using the pseudo-risk correction procedure outlined by Wald et al. (27) the estimated detection rate in twins was 52–55%, i.e. some 15% lower than in singleton pregnancies, for the same false-positive rate of 5% (28).

In the first trimester few data are available on the behavior of biochemical markers in twin pregnancies. Free beta-HCG levels may be elevated above that in the second trimester, while for pregnancy-associated protein A (PAPP-A) the level is slightly lower (1.8 MoM). Whether the detection rate in the first trimester can be increased above that in the second trimester remains to be shown.

Ultrasound screening

In singleton pregnancies screening by maternal age and fetal nuchal translucency (NT) can identify about 80% of chromosomally abnormal fetuses for an invasive testing rate of 5% (29).

In the only large twin pregnancy study the NT was above the 95th centile of the normal range in 65 out of 896 fetuses (7.3%), including seven of eight with trisomy 21 (30). In the chromosomally normal twin pregnancies the prevalence of increased NT was higher in fetuses from MC (8.4%) than DC pregnancies (6.9%). This study thus suggests that the DS detection rate may be similar in twin and singleton pregnancies, but the false-positive rate is higher in twin pregnancies, especially in MC pregnancies.

It may be concluded that it is possible to screen twin pregnancies for DS in the first as well as in the beginning of second trimester. The sensitivity of biochemical screening is 10–15% lower than in singleton pregnancies for the same false-positive rate, while NT screening yields the same detection rate but at a 50% higher false-positive rate than in singleton pregnancies. The additional advantage of NT screening is that when one of the fetuses is found to have a chromosomal abnormality and the other is normal, the presence of a sonographically detectable marker ensures the correct identification of the abnormal twin, should the parents choose to have a selective termination of pregnancy.

Further data are required regarding the performance of a screening combining biochemistry and ultrasonography, but the addition of maternal serum biochemistry to NT could be expected to increase the detection rate by a further 5–6% (31).

Invasive prenatal diagnostic tests

The efficacy and safety of second-trimester amnio- centesis (AC) and first-trimester chorionic villus sampling (CVS) will be examined first, the question of selective termination later. CVS is as effective as AC in providing sufficient tissue for accurate diagnosis (32). One concern about CVS is that there is no method available to confidently assess the source of chorionic villi. In cases of same-sex twins sampled by CVS, there is no guarantee that each twin was individually sampled. Therefore each chorion frondosum must be accurately and meticulously identified before and during CVS sampling. Even so, there is uncertainty in about 5% of CVS procedures that both placentas have been sampled, as compared to 0.3% of AC (32). During AC, aspiration of separate gestational sacs can be confirmed by injecting a coloring agent such as indigo carmine into the first sac. This dye has never been associated with any fetal or neonatal complications. Another dye, methylene blue, increased the risk of fetal death by a relative risk of 8.5 in an Australian study of 262 twins (33). Furthermore, a causal relationship between in utero methylene blue exposure and jejunal atresia was strongly suggested in a study of 89 twin pregnancies (34). The advent of real-time ultrasound has made dye injection obsolete in nearly all cases, since it allows visually guided amniotic fluid sampling from both sacs.

Sampling MC twin pregnancies presents unique problems. Although theoretically most MC pregnancies require only a single sampling, exceptions do occur in cases of heterokaryotypic twins or when the ultrasound impression of a single chorion is incorrect.

The spontaneous abortion rate in ultrasonographically normal twin pregnancies not under-
going an invasive procedure is poorly documented in the literature. Sebire et al. reported that 12.7% of 102 MC pregnancies detected before 15 weeks of gestation miscarried at least one fetus, while in the 365 DC pregnancies the rate was 2.5% (30). The spontaneous abortion rate in twin pregnancies thus seems to be higher than in singletons.

The procedure-related risk of fetal loss is about 1% after AC at 16–20 weeks of gestation (35), as well as after first trimester CVS (36) in singleton pregnancies. Because twins have a higher spontaneous abortion rate than singletons, the most appropriate control group would consist of twin pregnancies of the same gestational and maternal age not undergoing an invasive procedure. The studies on the risk of invasive prenatal diagnostic procedures in twin pregnancies all have significant limitations: some did not have complete follow-up, most are small-uncontrolled studies or studies using singleton pregnancies as controls, and a randomized study has not been conducted (37–41).

These factors can explain the wide variation in reported post-procedural fetal loss rates (Table I).

As the number of instrumental insertions in AC as well as CVS in singletons has been associated with an increase in procedure-related fetal losses (NICHD 1977) (42), it has been suggested that these procedures in twin pregnancies should be performed by a single insertion. This was shown to be successful in 48 of 55 pregnancies having AC (43), but the study was unfortunately too small to draw any conclusions concerning the risk of fetal loss. The risk of an invasive prenatal diagnostic procedure in twin pregnancies resulting from multi-fetal pregnancy reduction does not seem to differ from that in non-reduced twin pregnancies (44, 45).

It may thus be concluded that it is difficult to judge the extent to which the miscarriage rate following an invasive procedure in twin pregnancies is causally linked to the test. A cautious estimate may be that it is between the same and twice the risk in singleton pregnancies. There does not seem to be a great difference between the fetal loss rate after AC and CVS. The fact that sampling accuracy in twin pregnancy is higher when AC is chosen, speaks in favor of AC. However, the method of choice for invasive prenatal diagnosis must be seen in relation to the risk associated with selective termination.

### Selective termination

Selective termination is a procedure in which an abnormal fetus in a multifetal pregnancy is terminated in order to allow the pregnancy to continue to term with the normal fetus(es). Multifetal pregnancy reduction, on the other hand, is the elective reduction of three or more fetuses to a smaller number of fetuses in an attempt to reduce the mortality and morbidity of the surviving fetuses. Both these procedures present complex ethical and moral dilemmas for the parents and for the obstetrician.

When a structural malformation or chromosomal abnormality is diagnosed in one twin, the parents have the options of continuing the entire pregnancy, terminating the entire pregnancy or of selective termination of the affected fetus. With rare exceptions, a selective termination is not offered when the fetal anomaly is lethal, as selective termination has the potential of causing loss of the entire pregnancy. On the other hand the presence of a fetus with a major anomaly seems to increase the risk of preterm delivery (46). Twin pregnancies complicated by a fetus with a major anomaly will, on average, be delivered two weeks earlier than other twin pregnancies, resulting in a lower birth weight and associated risks of prematurity for the unaffected twin. Therefore selective termination should be included in the management options in cases of non-lethal, major anomalies in one twin.

The failure of the initial attempts at performing selective termination may have been due to the fact that they were performed in MZ twins with a shared placenta. In such cases the death of one fetus results in exsanguination of the remaining fetus. Currently selective termination in MC twins

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<th>Table I. Miscarriage rate following invasive prenatal diagnostic tests in twin pregnancies</th>
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<td><strong>Miscarriage rate</strong></td>
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<td>N</td>
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<td>Twins with AC compared to singletons without AC</td>
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<td>Twins with AC compared to twins without AC</td>
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<td>Twins with CVS compared to twins without CVS</td>
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<td>Twins with AC compared to twins with CVS</td>
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AC: amniocentesis. CVS: chorionic villus sampling.

can be achieved by umbilical cord ligation under ultrasound guidance or by fiber-optic fetoscopy (47). Obviously selective termination for DC twins has a better chance of succeeding, and has been shown to be technically successful in virtually 100% of cases (48). In DC pregnancies the benefits expected from selective termination should be weighed against the potential risk of the procedure concerning the unaffected twin (49). Selective termination can be done by several methods, intracardiac or intrafunic injection of KCl appears to cause a lower miscarriage rate (8.3%) than air embolization (41.7%) (48).

In 1994 a collaborative report from 9 centers on 169 twins (48) showed that the gestational age at the time of the procedure correlated positively with loss rate and inversely with gestation at delivery. In fact when the procedure was performed before 16 weeks 5.4% of the pregnancies were lost, while 14.4% of the pregnancies were lost when the procedure was performed after 17 weeks. In 1999 a larger collaborative report, partly from the same centers (50), presented data on 345 selective terminations in twins from 8 centers. The spontaneous abortion rate before 24 weeks was 7.0% and 80% of all viable deliveries occurred after 33 weeks. There was no longer any correlation between the gestational age at the time of the procedure and the loss rate, nor with the gestational age at delivery.

It thus seems that, with increasing experience, there has been a plateauing of risks and flattening of the gestational age curve. This underlines the importance of centralizing these procedures. Early prenatal diagnosis may still be optimal, however, to ensure the correct diagnosis of chorionicity without which selective termination cannot be done safely.

Miscarriage and perinatal mortality

In a large registry study, which could not distinguish between DC and MC pregnancies, the perinatal mortality rate was 5–6% higher in twins than in singletons (51). Perinatal statistics will, however, underestimate the contribution of MC placentaion to fetal death, since the highest mortality rate in MC pregnancies is before 24 weeks (Fig. 2). In a prospective study (52), at least one fetal loss occurred before 24 weeks of gestation in 12.7% of the 102 MC and 2.5% of the 365 DC pregnancies, and there was at least one perinatal loss after 24 weeks in 4.9% of MC and 2.8% of DC pregnancies. This study confirms that the miscarriage rate, as well as the perinatal mortality, is higher in twins than in singletons, and especially among MC twins.

Preterm delivery

Preterm delivery is the major cause of mortality and morbidity in twin pregnancies. In a large Californian multicenter study the preterm delivery rate (<32 weeks) was 15–17% among 432 twin pregnancies as compared to 1–2% in 33,451 singleton pregnancies. Furthermore, although only 2.6% of the fetuses were twins, they accounted for 9.5% of all stillbirths, 15.4% of all neonatal deaths and 12.2% of all perinatal deaths (53).

There is some evidence that sonographic assessment of the cervix can predict singleton pregnancies at high risk of preterm delivery. Iams et al. conducted (54) a multicenter study measuring cervical length at 24 and 28 weeks gestation in 2915 unselected women. The relative risk of preterm delivery increased with decreasing length of the cervix. The sensitivity of the test does, however, appear to be lower in symptom-free low-risk patients than in patients with symptoms of preterm labor (55).

In 215 twin pregnancies assessed in week 23 (56) the risk of preterm delivery increased exponentially with decreasing cervical length, just as in singletons (54, 57). Two studies have tried to find
the optimal cut-off in cervical length. In 85 women with twin pregnancies, the positive predictive value of a cervical length greater than 35 mm at 24–26 weeks for delivery at term was 97%. A cervical length of ≤25 mm, however, only identified 31% of those who delivered preterm at or before 33 weeks (58). Similarly Goldenberg and co-workers (59) found that the specificity for preterm delivery of a cervical length ≤25 mm in week 23 was 86% in 147 twin pregnancies, while the sensitivity was 54%. When the ultrasound scan was done in week 27 the sensitivity increased to 63%, but the specificity decreased to 69%. A single transvaginal examination at 23–26 weeks thus seems able to identify most twin gestations at low risk of preterm birth. However, the most important issue is to be able to detect those pregnancies at high risk of delivering preterm, and the sensitivity may increase with gestational age. In women admitted with signs of preterm labor between 23 and 33 weeks of gestation, the cervical length was a better predictor of preterm delivery than funneling or digital examination in singletons as well as twin pregnancies (60). Measurement of cervical length may thus be useful not only as a screening but also as a diagnostic method.

Cerclage reduced the risk of preterm labor ten times in singletons with cervical length below 20 mm at 23 weeks (61). This treatment is now being evaluated in a randomized controlled trial in singletons as well as in twin pregnancies.

**Monoamniotic twins**

Monoamniotic twins are the least common form of twin placentaion (1–2%), but have the highest fetal mortality rate (30–70%). Cord entanglements as well as acute forms of TTTS cause the majority of the fetal losses.

Cord entanglement can be demonstrated by Doppler examination in the first trimester (62), but will, however, be present in most cases. It has been suggested that the larger the fetuses, the smaller the risk of cord compression causing fetal death. Stabilization of fetal position has been attempted by administration of ‘Sulindac’ to the mother in order to reduce amniotic fluid volume and thereby the risk of cord compression (63). All six pairs of twins in this study were delivered without complications.

When monoamniotic twins are diagnosed, the parents should be counseled about the high risk of fetal death. If the pregnancy is continued, it should be intensively monitored and delivery appropriately timed. Evidence regarding the optimal time of delivery is lacking, most opt for delivery around 32–34 weeks.

**Fetal growth abnormalities**

The incidence of fetal growth restriction is significantly increased in twins compared to singletons. The main factors determining fetal growth are genetic potential and placental function, which is thought to be due mainly to the trophoblast invasion of the maternal spiral arteries. In MC pregnancies both the genetic potential and the trophoblast invasion should be the same, whereas in DC pregnancies there may be differences in the genetic constitution of the fetuses and of the placenta.

Abnormal growth in twin pregnancies may be detected by identifying growth discordance or small for gestational age (SGA) children (defined as birth weight 2 standard deviations or more below the mean for gestational age) (64). The most accurate assessment of fetal growth discordance is to compare abdominal circumferences. After 24 weeks an intertwin abdominal circumference difference of 20 mm or more, irrespective of gestational age, had an 83% positive predictive value to detect a difference in birth weight of 20% or more (65–67). Early second-trimester inter-twin weight discordance, however, was not correlated to birth weight discordance (26), but may instead be the consequence of a genetic defect or impaired placentation.

In order to find the SGA fetuses, their weight has to be compared to a norm. It is well known that the fetal weight of twins is close to that of singletons up to 30 weeks (68). After that time the overall pattern of fetal growth is slower for twins compared to singletons (69). Min et al. (69) have developed a birth weight reference for twins according to chorionicity, sex and race on the basis of longitudinal measurements, which maybe should be used to assess SGA in twins in the future.

The risk of growth retardation was about four times higher in MC (7.5%) compared to DC (1.7%) pregnancies (52). This finding is dependent on the reference or standard used, and the difference may be smaller if based on a chorionicity-dependent reference.

In a historic cohort study of 903 twins, Grobman & Parilla (70) demonstrated that the positive predictive value of a 20–24 weeks weight estimation to identify SGA infants was 85%.

Among infants with normal weight the elapsed time until a growth abnormality was detected was 10 weeks. This underlines the importance of the 20–24 week scan, since it may predict which infants will become SGA.

Several studies have suggested that discordance in umbilical artery flow is associated with growth discordance in twins and can identify those fetuses...
at high risk for unfavorable outcome (71, 72). Studies of the middle cerebral arteries permit assessment of redistribution of blood flow under conditions of fetal distress, where the brain sparing effect occurs. MC twins more often had brain-sparing effect than the DC twins, even in the MC group without TTTS (73–75). This may be one explanation for the higher mortality and morbidity seen in the MC group.

Twin-twin transfusion syndrome

The twin-twin transfusion syndrome (TTTS) complicates 5–15% of all MC twin pregnancies (52). It is one of the most lethal conditions in fetal medicine with an 80–100% mortality rate without treatment (76) and a 15–50% risk of handicap in survivors (4).

Pathogenesis

Cross circulations may be found in both MC and DC placentas, but the TTTS is a phenomenon of MC twins and is only very rarely seen in MZ DC twins. The classic concept of the pathogenesis has been that it is caused by a simple shift of blood from the donor twin to the recipient. More recently it has, however, been suggested that placental vascular anastomoses in twins with TTTS are fewer, more often solitary and of the arteriovenous type than in twins without TTTS (4). This hypothesis is supported by histopathological studies from Canada, where all MC twins with unidirectional a-v anastomoses in the absence of superficial anastomoses developed TTTS as compared to only 11% among the twins with several superficial anastomoses (77). TTTS may thus be the result of a paucity of bi-directional superficial anastomoses making some MC twins unable to compensate for the hemodynamic imbalance resulting from the unidirectional transfusion along the arterio-venous anastomosis.

Through the vascular anastomoses, one of the fetuses becomes a donor and gradually develops anemia, hypovolemia, hypertension and growth retardation, whereas the recipient becomes hypervolemic, hypertensive and macrosomic with increased urinary output. The discrepancy in blood volume results in oliguria with consequent anhydramnios in the donor and polyuria with consequent polyhydramnios in the recipient. Signs of hydrops fetalis are occasionally found in the recipient twin, rarely in the donor and seldom in both.

The most bizarre form of intertwin transfusion is the Reverse arterial perfusion (TRAP): One twin (the pump) actively perfuses the acardiac co-twin via retrograde flow. Typically the pump twin is structurally normal, but at high risk of developing cardiac failure. The mortality without treatment is greater than 50% (78).

Diagnosis

The first sign is a marked discordance in amniotic fluid volume in MC twins (79, 80). An estimation of amniotic fluid volume is therefore used to assess the well being of both twins. An amniotic fluid index above 40 cm or a deepest vertical pocket above 12 cm in the larger sac seems to select severe cases (81).

Discordance in size with the larger twin in the polyhydramniotic sac is usually seen. In most cases the donor appears as the stuck twin, fixed to the placenta or uterine wall by the intertwin membrane because of anhydramnios, while the recipient has polyhydramnios. The donor’s bladder is small or empty, while the recipient shows signs of polyuria with a distended bladder. Doppler ultrasonography is used to assess fetal well-being. Absent or low-end diastolic velocities in the umbilical artery are signs of increased placental resistance. Poor prognostic factors include reverse flow in the umbilical arteries, reduced pulsatility index in the middle cerebral arteries as a sign of fetal blood flow redistribution and pulsatile flow in the umbilical vein, reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein. Decreased ventricular function, tricuspid regurgitation and cardiac chamber enlargement are commonly seen in the recipient (82). In severe cases the recipient develops non-immune hydrops and tricuspid incompetence (74). Fetal echocardiography (83) should therefore be performed, since the perinatal prognosis of the recipient twin depends on the severity of the cardial disease.

Recently a classification of TTTS has been advocated in order to individualize the therapeutic options and to allow comparison of outcomes from different centers (84) (Table II).

Prediction

Three methods seem to have the potential to predict which MC twins are at increased risk of developing TTTS. As early as in week 10–14 an increased NT may be a sign of TTTS. The likelihood of developing severe TTTS was 4.4 (95% confidence interval 1.8–9.7) among those MC twins with a NT above the 95th centile (85).

Identification of arterio-arterial anastomoses by color Doppler on the placental plate may detect a low risk group in which only 5% developed TTTS. In twins without a-a anastomoses, on the other hand, TTTS was diagnosed in 58% (86). The an-
Twin pregnancy

Table II. Staging of TTTS based on sonographic and Doppler findings (modified after Quintero et al., (ref. no. 84)

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<thead>
<tr>
<th>Stage</th>
<th>Donor</th>
<th>Recipient</th>
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<tr>
<td>1</td>
<td>Oligohydramnion</td>
<td>Polyhydramnios</td>
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<td></td>
<td>Bladder still visible</td>
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<tr>
<td>2</td>
<td>Bladder not visible</td>
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<td>3</td>
<td>Abnormal Doppler indices*</td>
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<tr>
<td>4</td>
<td>Hydrops</td>
<td>Hydrops</td>
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<tr>
<td>5</td>
<td>(Fetal demise)</td>
<td>Fetal demise</td>
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* Abnormal Doppler indices: absent end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus or pulsatile umbilical venous flow usually with tricuspid regurgitation.

TTTS: Twin-twin transfusion syndrome.

giovessioarchitecture was confirmed by postnatal injection. This study confirmed the theory associating a paucity of superficial anastomoses in MC twins with TTTS. Further prospective studies are indicated to determine the utility of color Doppler to predict the risk of TTTS.

The most promising sign may be the folding of the intertwin membrane at 15–17 weeks, caused by the disparity in amniotic fluid volume in the two amniotic sacs (87). In a prospective study of 83 MC twins, there were 23 cases with membrane folding (28%), half of which developed severe TTTS, while the rest developed mild TTTS. All 60 pregnancies without membrane folding resulted in live births without signs of TTTS.

Management

Serial therapeutic amniocenteses may relieve polyhydramnios and thereby prevent preterm labor (88–91). The reduction in amniotic fluid pressure may also improve the perfusion to the donor. It has been suggested removing approximately one litre of amniotic fluid for every 10 cm the Amniotic Fluid Index is elevated (91). Serial aggressive amnioreduction is associated with an overall perinatal survival rate around 65% (92), but with a 15–50% risk of serious handicap in the survivors (93).

More recent developments in the management of TTTS are fetoscopy and laser coagulation to interrupt the placental vascular anastomoses between the twins. Under continuous ultrasound and fetoscopic visualization the chorionic plate along the inter-twin membrane is examined to identify the crossing vessels, which are then coagulated with a laser beam. Subsequently amniotic fluid is drained to obtain a subjective normalization of the amniotic fluid volume. Theoretically coagulation of the specific vessels (a-v anastomosis) should alleviate TTTS. However, coagulation of several vessels seems to protect the survivor if the other twin dies in utero. In a multi-center study endoscopic laser was carried out at a median of 21 weeks and the perinatal survival for both twins was 55% and 73% for at least one surviving child (94).

These results are comparable to serial amniocenteses, but the handicap rate in survivors appeared lower. In a more recent German study (95) the results from one center performing laser surgery in 73 twin TTTS pregnancies were compared to 43 twin TTTS pregnancies treated with amniotic drainage. The overall survival rate was the same in the two groups, but there were a significantly higher proportion of pregnancies with at least one survivor in the laser group (79% versus 60%). The incidence of abnormal neonatal brain scans was significantly lower among survivors in the laser group (6%) than in the amniocentesis group (18%). This may be due to the protective effect of coagulating the communicating vessels, combined with a higher gestational age at delivery. The results of laser surgery appear better than serial amniocenteses, but have so far only been evaluated in observational studies. An on-going multi-center European randomized controlled trial will determine whether the results of laser surgery are superior to serial amniocenteses.

A new non-invasive technique, focused ultrasound surgery, may become a non-invasive method to occlude placental vessels (96).

Selective feticide of one twin may be considered in those cases, where one of the twins appears to be at imminent demise or once other treatment has failed to try to salvage the co-twin. Selective reduction should involve an occlusive technique to prevent any possibility of the surviving twin exsanguinating into the terminated twin’s circulation. Intrauterine ligation of one umbilical cord and bipolar coagulation have been shown to be feasible, but these procedures should still be considered investigational (47, 97–99).

Non steroid anti-inflammatory drugs have been used as a treatment for polyhydramnios in singletons, as they reduce fetal urinary output. They are, however, contraindicated in twins with TTTS, because they have a harmful effect on the oligouric donor twin (100).

Neurological damage in twins

Death of one twin in a MC pregnancy is associated with a 25% risk of demise for the co-twin or at least a 25% risk of neurological and/or renal lesions in the survivor (101, 102). Antenatal cerebral white matter lesions seem to be more common in MC twins both with and without TTTS.
Table III. Recommendations for ultrasonographic evaluation of twin pregnancies

<table>
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<th>Gestational week</th>
<th>Examination</th>
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| Before week 15    | • Determination of chorionicity  
                  | • Measurement of nuchal translucency in both twins  
                  | • Measurement of CRL in both twins |
| In week 16–25     | Control of MC twins every other week for:  
                  | • Folding sign, and the a-a anastomoses  
                  | • Signs of TTTS (Amnion fluid volume, the bladders of the fetuses, hydrops) |
| In week 18–20     | Check for structural anomalies for both MC and DC |
| In week 21–22     | Fetal echocardiography for both MC and DC |
| In week 23        | For both MC and DC:  
                  | • Assessment of cervical length  
                  | • Measurement of the abdominal circumference of both fetuses  
                  | • Determine the weight discordance |
| From week 28 to delivery | Growth assessment and rule out discordance |


compared to DC twins as well as singletons (103), and in both the recipient and the donor TTTS twin (104).

The risk for the co-twin in MC pregnancies to a large extent depends upon the vascular anatomy of the monochorionic placenta. The precise mechanism of the co-twin compromise is unclear, but is probably the consequence of a hemodynamic imbalance resulting from a lack of placental anastomoses. A dying twin gives rise to a fall in blood pressure, and blood from the survivor is transfused into the fetoplacental circulation of the dead twin, causing severe hypotension and irreversible brain damage in the survivor (105, 106). Conservative management (101) after fetal death of one twin in TTTS has a very poor prognosis and supports the concept of active management.

At 24 weeks infants with normal weight have a 40% chance of survival, compared to 80% at 28 weeks. The prognosis is much worse, both in relation to perinatal mortality and in relation to neurological damage, when the fetuses are SGA or pathological Doppler velocities are found in the umbilical arteries (107).

In conclusion, this literature review leads us to suggest the following examination program for twin pregnancy (Table III).

References


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Twin pregnancy


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