

Chapter 5 - MULTIPLE PREGNANCY

TYPES OF MULTIPLE PREGNANCY

Multiple pregnancy usually results from the ovulation and subsequent fertilization of more than one oocyte. In such cases, the fetuses are genetically different (polyzygotic or non-identical). Multiple pregnancy can also result from the splitting of one embryonic mass to form two or more genetically identical fetuses (monozygotic).

In all cases of polyzygotic multiple pregnancy, each zygote develops its own amnion, chorion and placenta (polychorionic). In monozygotic pregnancies, there may be sharing of the same placenta (monochorionic), amniotic sac (monoamniotic) or even fetal organs (conjoined or Siamese). When the single embryonic mass splits into two within 3 days of fertilization, which occurs in one-third of monozygotic twins, each fetus has its own amniotic sac and placenta (diamniotic and dichorionic) ([Figure 1](#)). When embryonic splitting occurs after the third day following fertilization, there are vascular communications within the two placental circulations (mono chorionic). Embryonic splitting after the 9th day following fertilization results in monoamniotic, monochorionic twins and splitting after the 12th day results in conjoined twins.

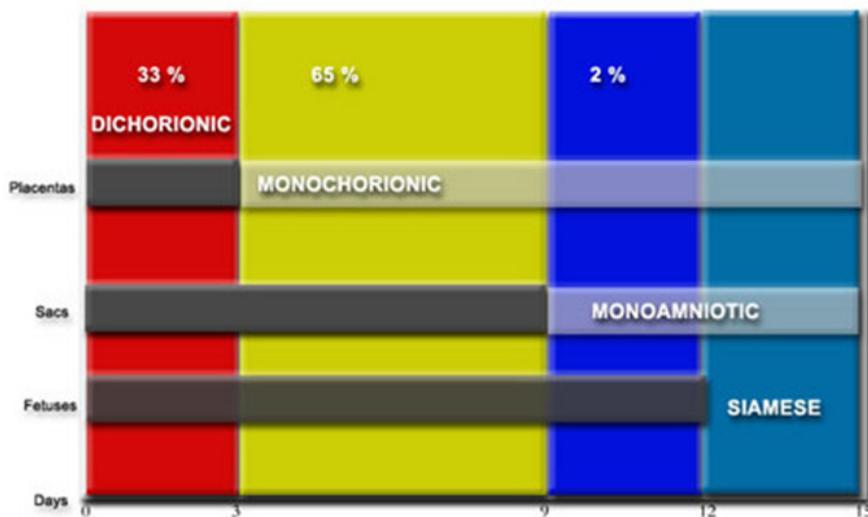
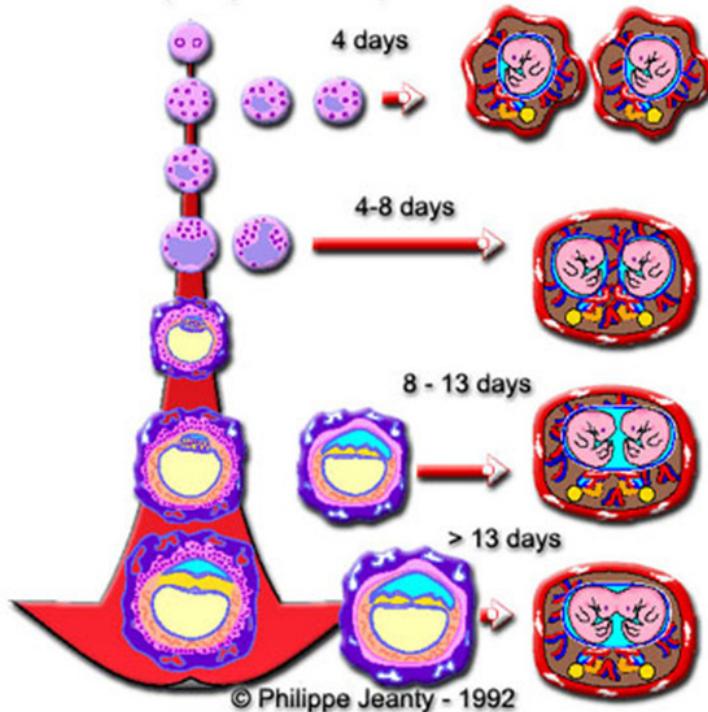


Figure 1 - In monozygotic twins, embryonic splitting within the first 3 days after fertilization results in a diamniotic and dichorionic pregnancy; splitting between days 3 and 9 results in a diamniotic, monochorionic pregnancy; splitting between days 9 and 12 results in a mono-amniotic, monochorionic pregnancy; and splitting after the 12th day results in conjoined twins



Schematic drawing demonstrating the outcome of twinning at different stages of early embryonic life

Top: Fission before the formation of the inner cell mass and any differentiation will produce two embryos with two separate chorions, amnions and placentas. Middle: Twinning at the early blastocyst stage, after formation of the inner cell mass, will cause the development of two embryos, with one placenta and one chorion but two separate amnions. **Bottom:** If separation occurs after the formation of the embryonic disc, the amnion has already formed, and will lead to a monoamniotic, monochorionic pregnancy. Incomplete fission at this stage or later will result in conjoined twins.

courtesy from Philippe Jeanty - www.thefetus.net

Type of Twins

Dizygotic twins (1/90):

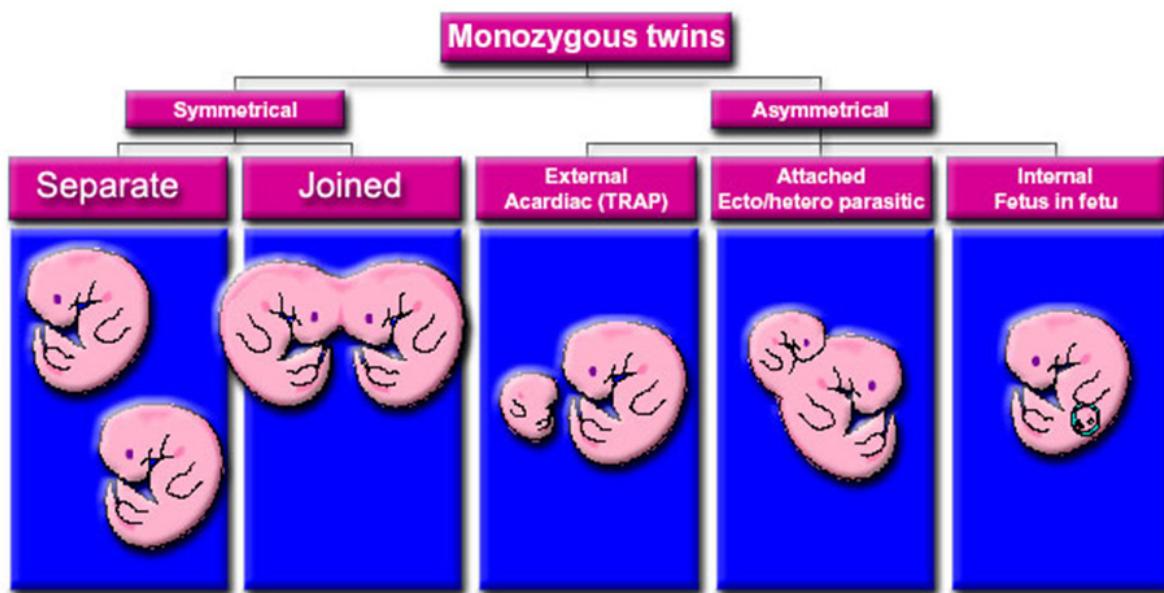
Superfecundation	Not the same father	Many case-reports in the literature of the last century
Superfetation	Not the same cycle	Historically these were misinterpretations of growth discordance, but recent DNA studies have demonstrated that the condition is occasionally possible, in particular with assisted reproductive techniques
Fraternal twins	Same father, same cycle	The usual twins

Monozygotic twins (1/250):

DiAmniotic DiChorionic	Same zygote, 2 separate sacs	Early separation
DiAmniotic MonoChorionic	Same zygote, 2 separate amnions	
MonoAmniotic MonoChorionic	Same zygote, same sac	Late separation
Conjoint	Equally but incompletely divided	Incomplete separation
Duplicata incompleta	Incompletely duplicated	
Ectoparasitic twin	Partial fetus attached to sib	Partial division
Fetus-in-fetu	Embedded	

courtesy from Philippe Jeanty - www.thefetus.net

A classification of monozygous twin according to their symmetry or lack of :



courtesy from Philippe Jeanty - www.thefetus.net



Ectoparasitic twins are parts of twins implanted in another fetus. In this case what appears to be an omphalocele on the left is a fetal abdomen with lower legs on the extreme left.
 (Courtesy Glynis Sack, MD, www.TheFetus.net)

INCIDENCE AND EPIDEMIOLOGY

Twins account for about 1% of all pregnancies, with two-thirds being dizygotic and one-third monozygotic. The incidence of dizygotic twins varies with ethnic group (up to 5 times higher in certain parts of Africa and half as high in parts of Asia), maternal age (2% at 35 years), parity (2% after four pregnancies) and method of conception (20% with ovulation induction). The incidence of monozygotic twins is similar in all ethnic groups and does not vary with maternal age or parity, but may be 2–3 times higher following *in vitro* fertilization procedures, possibly because with these methods the architecture of the zona pellucida is altered^{1,2}.

In the last 20 years, the rate of twinning has increased (Figure 2). The increase in dizygotic twins is mainly due to the widespread use of assisted reproductive techniques and the increasing maternal age. There has also been an increase in the rate of monozygotic twinning, particularly in those countries in which there is widespread use of oral contraceptives.

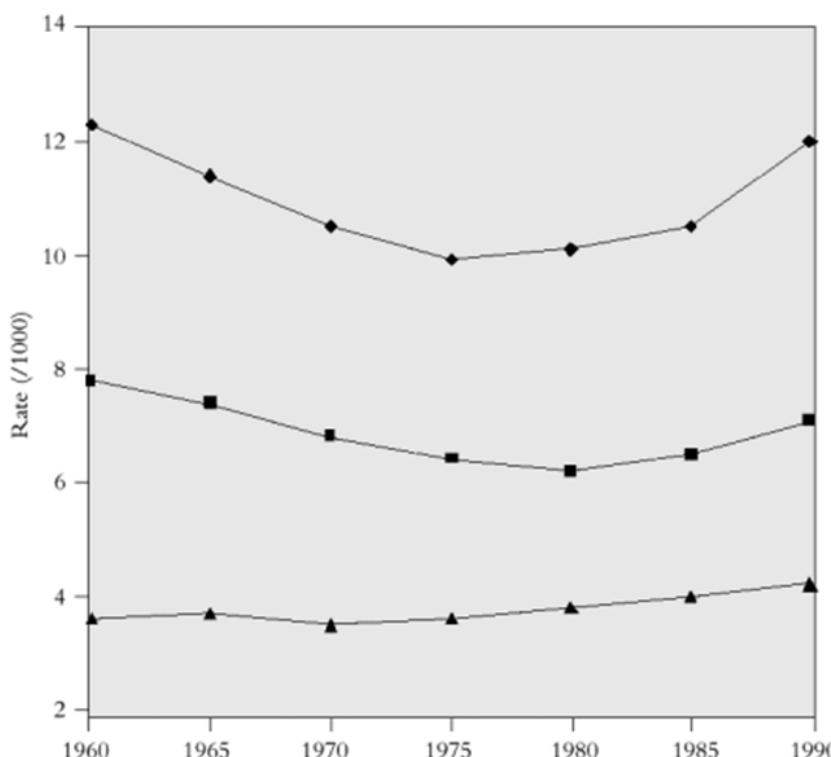


Figure 2 - Twinning rate (per 1000 pregnancies) in England and Wales, 1960–1990 for all twins (diamond markers), dizygotic twins (square markers) and monozygotic twins (triangle markers; adapted from Derom et al. 1995)

The incidence of spontaneous multifetal (more than two) pregnancies can be derived from Hellin's rule (1 in 80^{n-1} pregnancies, where n is the number of fetuses). In recent years assisted reproductive techniques, such as ovulation induction and *in vitro* fertilization, have become important causes of multiple pregnancies and the vast majority of multifetal pregnancies result from such treatments.

ZYGOSITY AND CHORIONICITY

Zygosity can only be determined by DNA fingerprinting. Prenatally, such testing would require an invasive procedure to sample amniotic fluid (amniocentesis), placental tissue (chorionic villus sampling) or fetal blood (cordocentesis).

Determination of chorionicity can be performed by ultrasonography and relies on the assessment of fetal gender, number of placentas and characteristics of the membrane between the two amniotic sacs. Different-sex twins are dizygotic and therefore dichorionic, but in about two-thirds of twin pregnancies the fetuses are of the same sex and these may be either monozygotic or dizygotic. Similarly, if there are two separate placentas, the pregnancy is dichorionic, but, in the majority of cases, the two placentas are adjacent to each other and there are often difficulties in distinguishing between dichorionic-fused and monochorionic placentas.

In dichorionic twins, the intertwin membrane is composed of a central layer of chorionic tissue sandwiched between two layers of amnion, whereas in monochorionic twins there is no chorionic layer. Consequently, the intertwin membrane tends to be thicker and more echogenic in dichorionic than monochorionic pregnancies, but this is a subjective and quite unreliable finding. For example, one study reported that dichorionicity is associated with an inter-twin septum thickness of 2 mm or more⁴, but the reproducibility of this measurement was poor and is dependent on such technical aspects as the angle of insonation and gestational age⁵.

The best way to determine chorionicity is by an ultrasound examination at 6–9 weeks of gestation, when in dichorionic twins there is a thick septum between the chorionic sacs ([Figure 3](#))^{6–8}. After 9 weeks, this septum becomes progressively thinner to form the chorionic component of the intertwin membrane, but it remains thick and easy to identify at the base of the membrane as a triangular tissue projection, or lambda sign^{9–11}.



Figure 3a - Dichorionic twin pregnancy at 7–8 weeks, demonstrating the thick septum.



Figure 3b - Dichorionic twin pregnancy at 7–8 weeks, demonstrating the thick septum (3D scan)

At 11–14 weeks of gestation, sonographic examination of the base of the inter-twin membrane for the presence or absence of the lambda sign ([Figure 4](#)) provides reliable distinction between dichorionic and monochorionic pregnancies. In an ultrasound study of 368 twin pregnancies at 10–14 weeks of gestation, pregnancies were classified as monochorionic if there was a single placental mass in the absence of the lambda sign at the inter-twin membrane-placental junction, and dichorionic if there was a single placental mass but the lambda sign was present or the placentas were not adjacent to each other¹¹. In 81 (22%) cases, the pregnancies were classified as monochorionic and in 287 (78%) as dichorionic. All pregnancies classified as monochorionic resulted in the delivery of same-sex twins and all different-sex pairs were correctly classified as dichorionic¹¹.

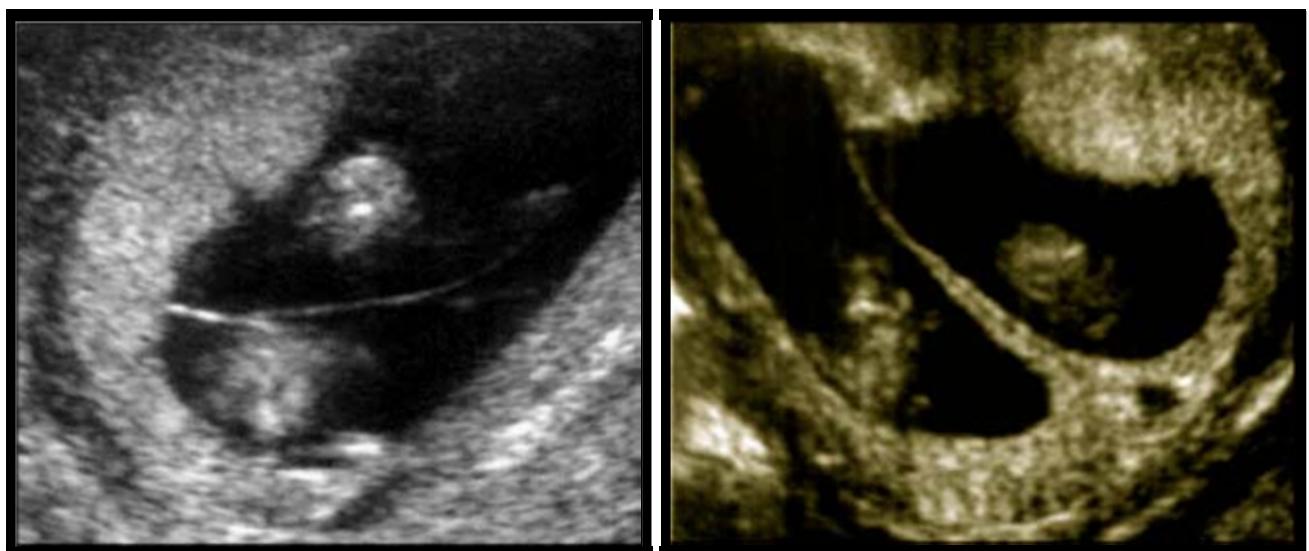
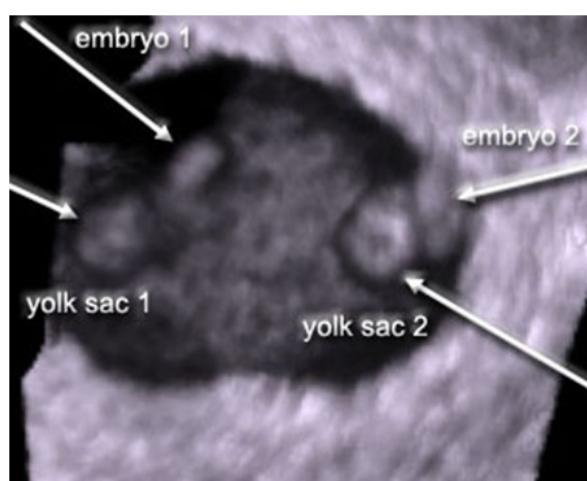
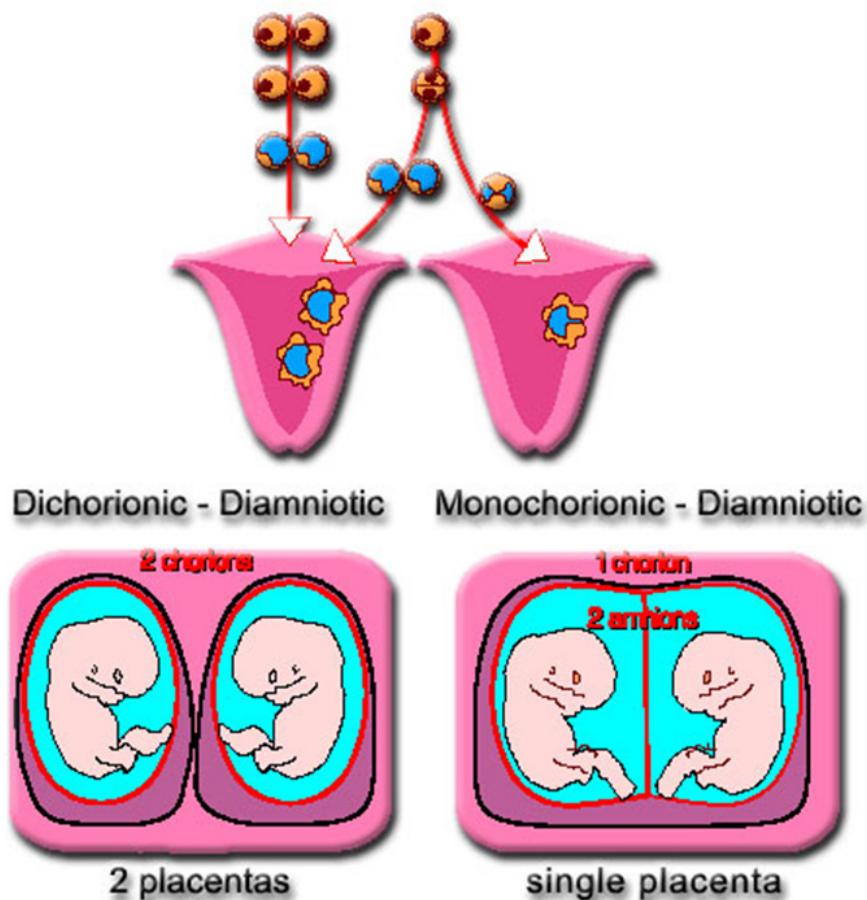


Figure 4 - Ultrasound appearance of monochorionic (left) and dichorionic (right) twin pregnancies at 12 weeks of gestation. Note that, in both types, there appears to be a single placental mass but in the dichorionic type there is an extention of placental tissue into the base of the intertwin membrane, forming the lambda sign



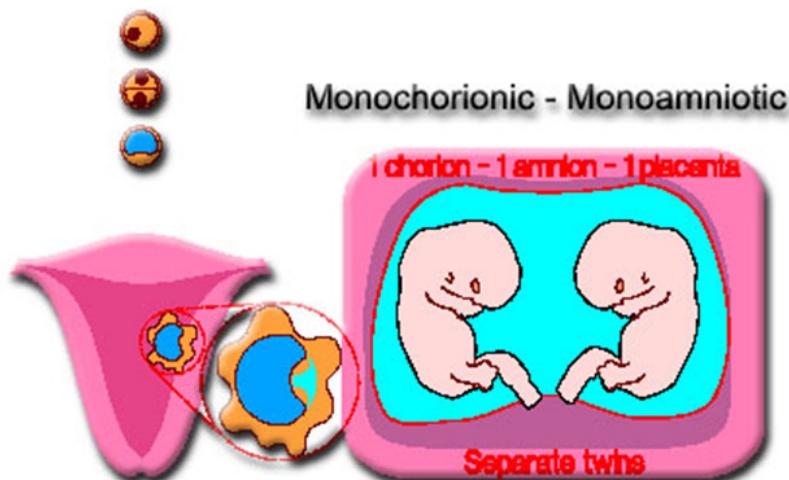
3D scan at 6 weeks Monochorionic – Diamniotic

Monochorionic Twin



The implantation of two fertilized eggs (left side of the drawing) will result in two gestational sacs that share neither the chorion nor the amnion. The drawing illustrates how the placenta can insert between the two sacs producing the "Lambda sign" (lambda sign). On the right side of the drawing, a single egg can either split early (before 4 days) into two embryos and the 2 embryos will then resemble the previous condition, or the fertilized egg can split between the 4th and 8th days at a time when the chorion is no longer divisible. Both embryos will then share the chorion, the placenta will not be able to infiltrate between the two gestational sacs and the membrane insertion will have the "T" appearance. The ultrasound images underneath the drawings illustrate the membrane insertion in both cases.

courtesy from Philippe Jeanty - www.thefetus.net

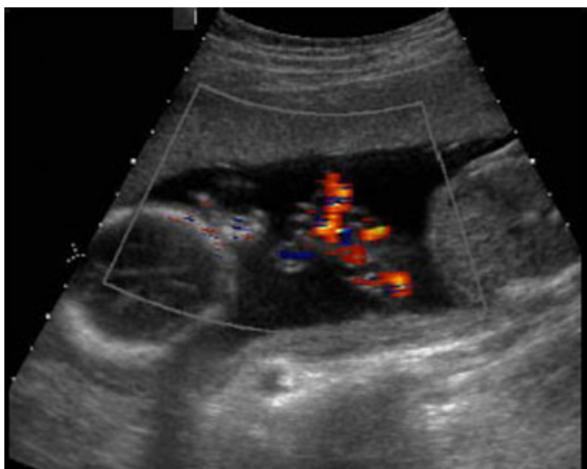


Sonographic features

- Single placenta and same sex twins;
- Close approximation of the cord insertions;
- Entanglement of the cords;
- Normal and identical amniotic fluid volume around both fetuses;
- Unrestricted fetal movement; and
- Absence of a dividing membrane demonstrated on two studies at least 12-15 hours apart.
- A single yolk sac may be a normal finding.



Absence of a dividing membrane between two fetuses that are intimately in contact.



Close approximation of the cord insertions

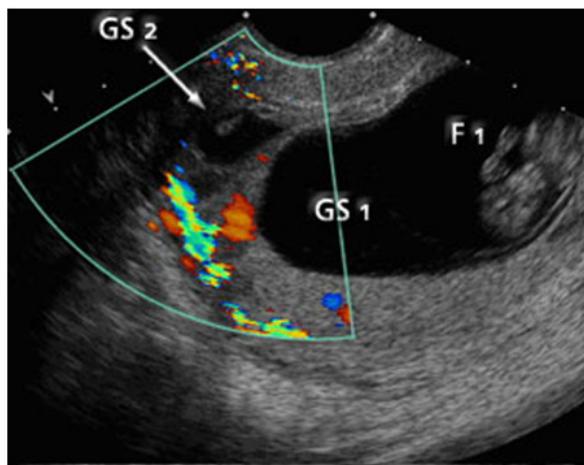
Evolution of the lambda sign with gestation

With advancing gestation, there is regression of the chorion laeve and the lambda sign becomes progressively more difficult to identify. A study examined 154 twin pregnancies for the presence or absence of the lambda sign at 10–14 weeks of gestation and again at 16 and 20 weeks¹². There were 101 twin pregnancies with a lambda sign identified at 10–14 weeks; at 16 weeks, the lambda sign was present in 98% of the cases and at 20 weeks in 87%. The lambda sign was subsequently identified in none of the 53 pregnancies in which it was absent at 10–14 weeks¹². Therefore, absence of the lambda sign at 16 or 20 weeks, and presumably thereafter, does not constitute evidence of monochorionicity and consequently does not exclude the possibility of dichorionicity or dizygosity. Conversely, because none of the pregnancies classified as monochorionic at the early scan subsequently developed the lambda sign, the identification of this feature at any stage of pregnancy should be considered as evidence of dichorionicity.

MISCARRIAGE AND PERINATAL MORTALITY

The perinatal mortality rate in twins is around 6 times higher than in singletons¹³⁻¹⁷. This increased mortality, which is mainly due to prematurity-related complications, is higher in monochorionic than dichorionic twin pregnancies. In monochorionic twins, an additional complication to prematurity is twin-to-twin transfusion syndrome. Thus, retrospective studies in which both zygosity and chorionicity were determined after birth reported that the perinatal mortality rate is about 3–4 times higher in mono chorionic compared to dichorionic twins, regardless of zygosity^{18,19}.

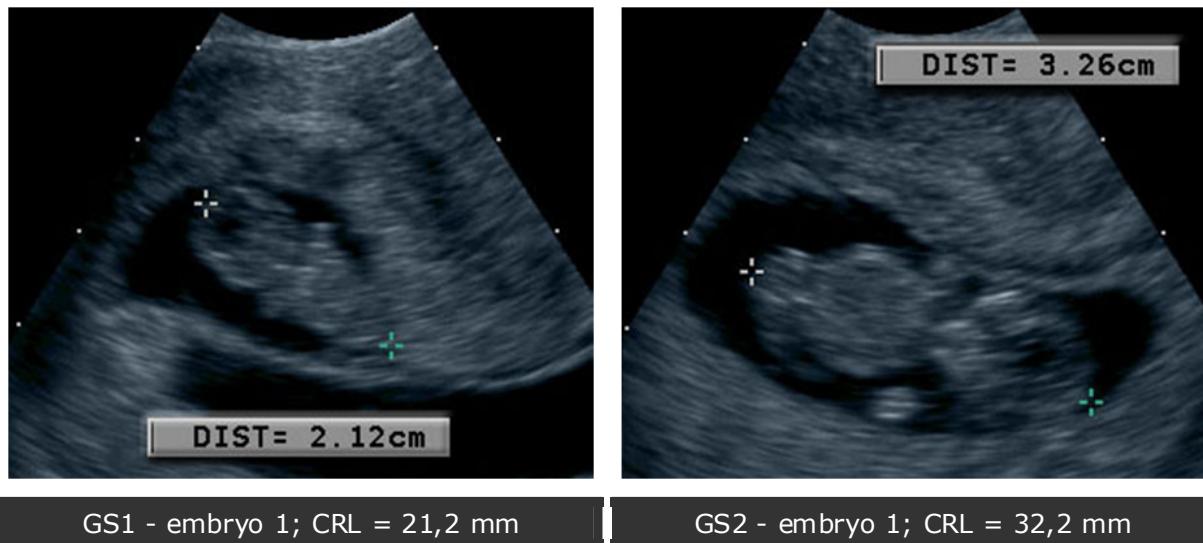
A prospective study, in which chorionicity was assessed by ultrasound examination at 10–14 weeks of gestation, compared pregnancy outcome in 102 monochorionic and 365 dichorionic twin pregnancies²⁰. There was at least one fetal loss before 24 weeks of gestation in 12.7% of monochorionic and 2.5% of dichorionic pregnancies. Additionally, there was at least one perinatal loss (at or after 24 weeks) in 4.9% of monochorionic and 2.8% of dichorionic pregnancies²⁰.



Dichorionic and Diamniotic pregnancy at 8-9 weeks gestation, with a embryonic loss inside gestational sac (GS2) and visualization of a live embryo inside gestational sac 1 (GS1)



Dichorionic and Diamniotic pregnancy at 9+2 weeks gestation, with a discrepancy of to embryos size.



This study confirmed that perinatal mortality in twins, especially those that are monochorionic, is higher than in singleton pregnancies. However, perinatal statistics underestimate the importance of monochorionic placentation to fetal death since the highest rate of mortality is before 24 weeks of gestation ([Figure 5](#))²⁰. This hidden mortality confined to monochorionic pregnancies is likely to be the consequence of the underlying chorioangiopagus and severe early-onset twin-to-twin transfusion syndrome. Therefore, reduction of the excess fetal loss in twins, compared to singletons, can only be achieved through early identification of monochorionic pregnancies by ultrasound examination at 11–14 weeks of gestation, and the development of appropriate methods of surveillance and intervention during the second trimester of pregnancy.

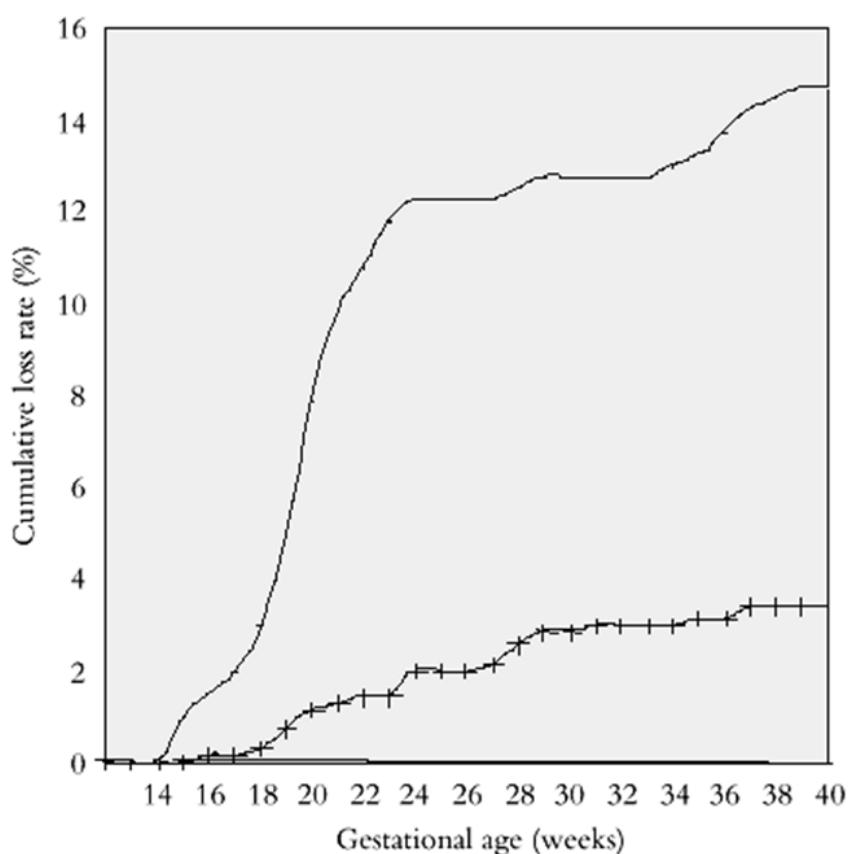
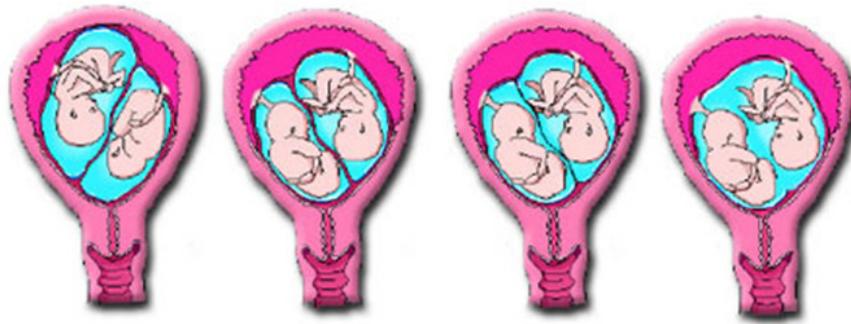


Figure 5 - Cumulative fetal loss rates in monochorionic (solid line) and dichorionic (dashed line) twin pregnancies, from 12 weeks of gestation²⁰

Frequency and mortality according to the types of placentation

(Liu S, Bernirschke K, Scioscia AL, Mannino FL. Intrauterine death in multiple gestation. Acta Genet Med Gemellol 1992;41:5-26.)



Diamniotic DiChorionic Separate placentae	Diamniotic DiChorionic fused placentae	Diamniotic MonoChorionic single placenta	Monoamniotic MonoChorionic single placentae
Frequency: 35%	27%	36%	2%
Mortality: 13%	11%	32%	44%

courtesy from Philippe Jeanty - www.thefetus.net

SEVERE PRETERM DELIVERY

The most important complication of any pregnancy is delivery before term, and especially before 32 weeks. Almost all babies born before 24 weeks die and almost all born after 32 weeks survive. Delivery between 24 and 32 weeks is associated with a high chance of neonatal death and handicap in the survivors. In a singleton pregnancy, the chance of delivery between 24 and 32 weeks is 1–2%. In a study of 467 twin pregnancies in which chorionicity was assessed during the 11–14-week scan, the median gestation at delivery of live births was only marginally earlier in monochorionic (36 weeks), compared to dichorionic (37 weeks) pregnancies²⁰. However, the proportion of pregnancies delivering very preterm (before 32 weeks) was nearly twice as high in monochorionic (9.2%) compared to dichorionic (5.5%) twins ([Figure 6](#))²⁰.

The extent to which close monitoring of cervical length and the insertion of cervical sutures in those with a short cervix will reduce the risk of severe preterm delivery remains to be determined.

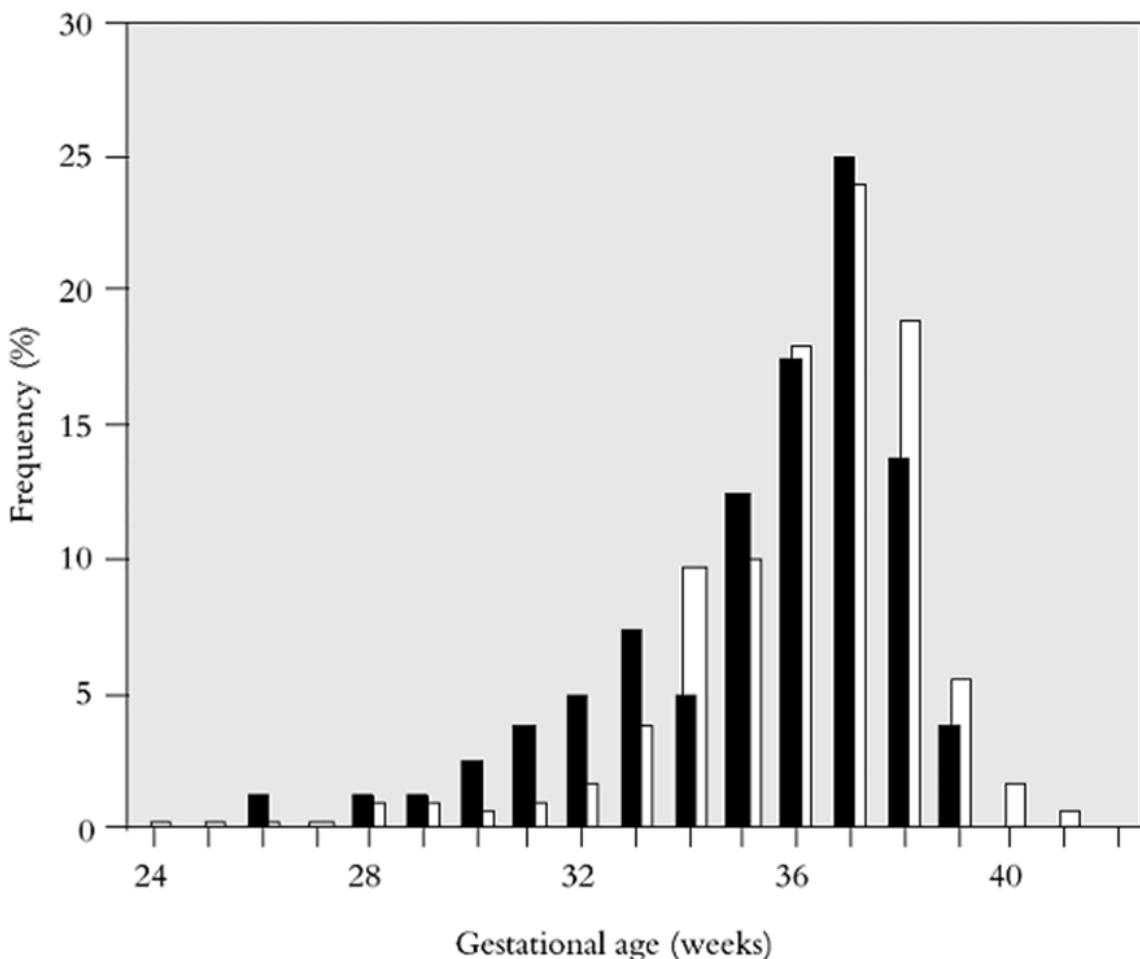


Figure 6 - Gestational age distribution at delivery of monochorionic (solid bars) and dichorionic (open bars) twin pregnancies. The proportion of pregnancies delivering very preterm (before 32 weeks) is considerably higher in monochorionic compared to dichorionic twins²⁰

Cervical Incompetence

by [Juan Carlos Quintero](http://www.thefetus.net) M. MD, Philippe Jeanty MD, PhD - from www.thefetus.net

Synonyms: Premature ripening of the cervix;

Definition: Condition in which the cervix fails to retain the conceptus during pregnancy. Cervix length less than 25 mm.

History: Lash described in 1950 cervical cerclage the treatment of cervical incompetence[1].

Prevalence: Affects 1% of pregnant patients[2].

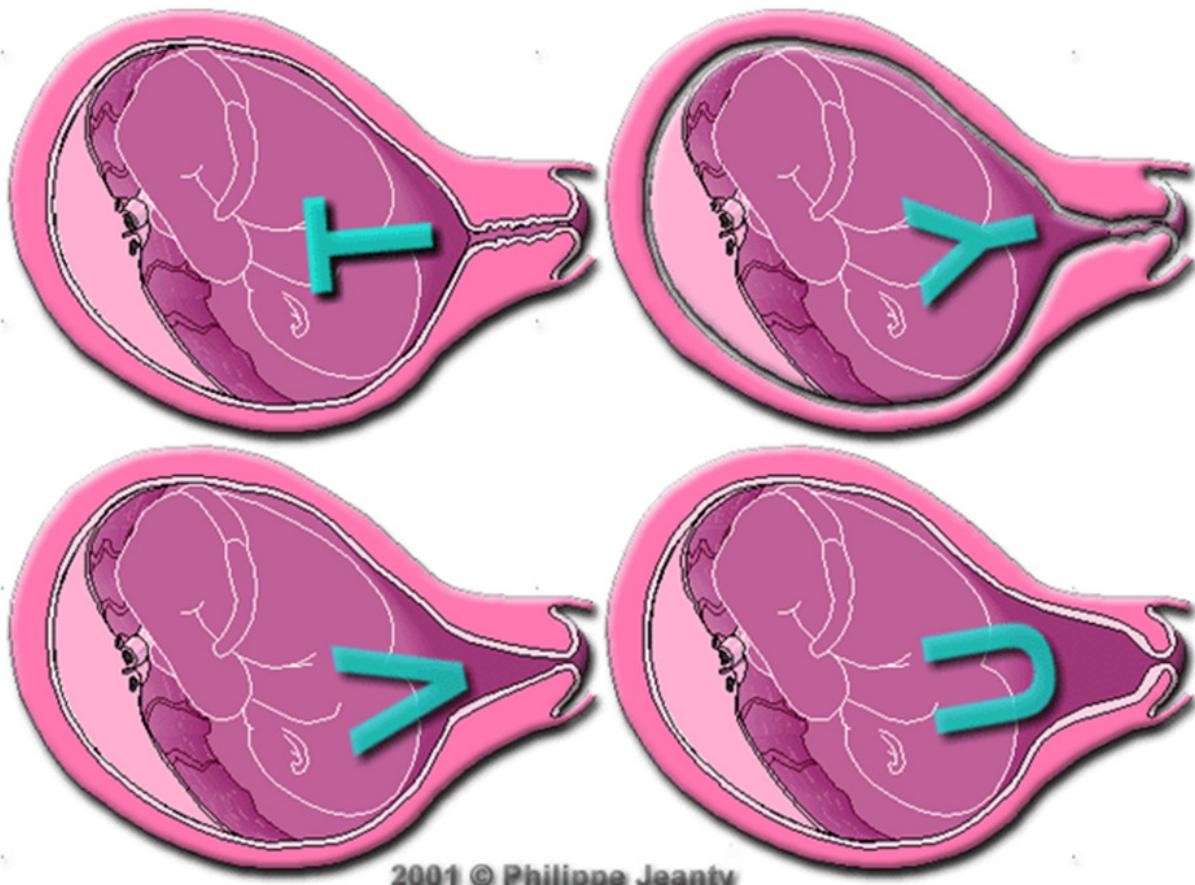
Etiology:

- Idiopathic (most)
- Congenital disorders (congenital mullerian duct abnormalities[3],
- DES exposure in utero[4]),
- Connective tissue disorder (Ehlers-Danlos syndrome[5])
- Surgical trauma (conization, resulting in substantial loss of connective tissue) or traumatic damage to the structural integrity of the cervix (repeated cervical dilatation associated with termination of pregnancies).

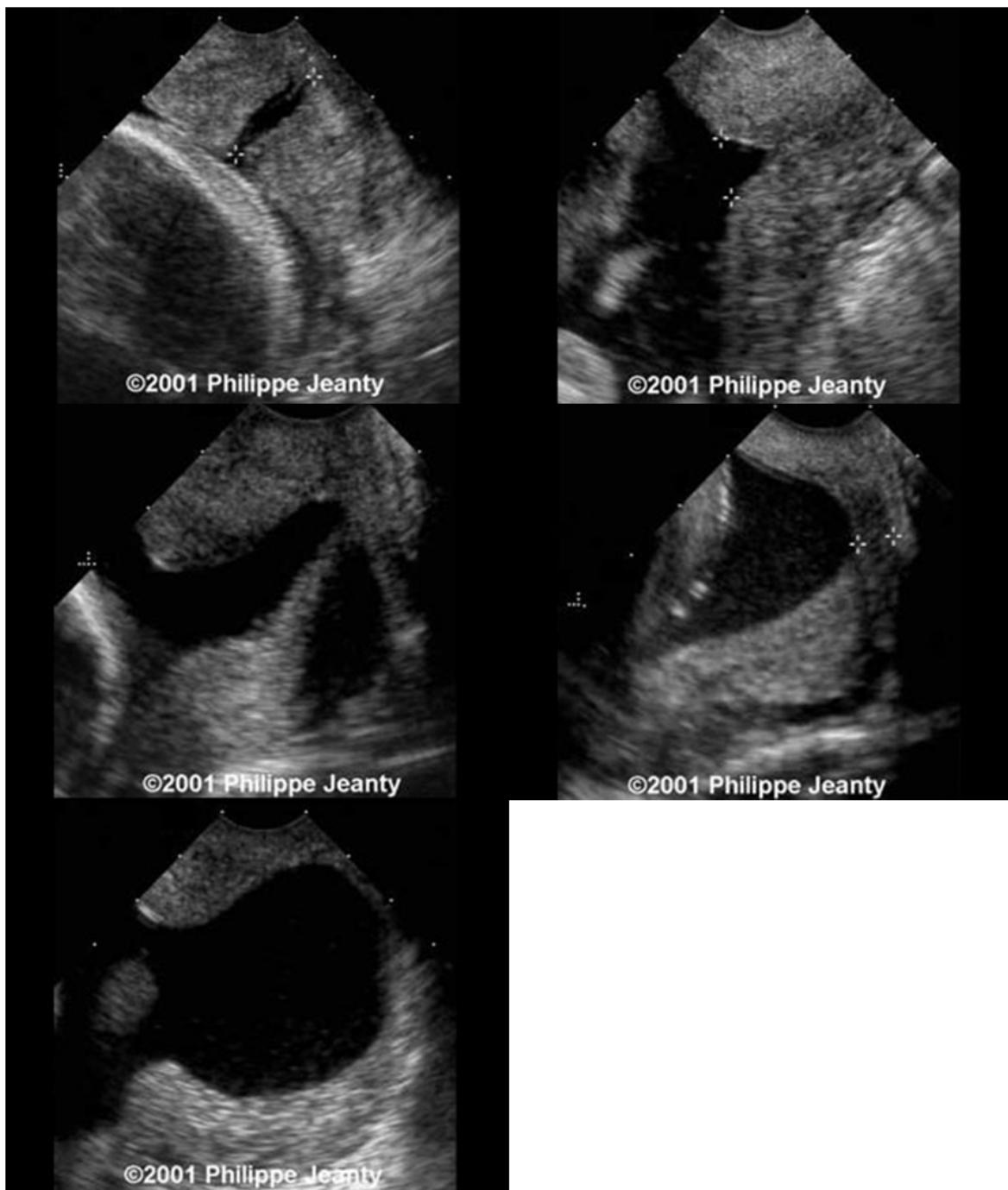
Pathogenesis: The function of the cervix during pregnancy depends on the regulations of connective tissue metabolism. Collagen[6] is the principal component in the cervical matrix, others are proteoaminoglycans, elastin and glycoproteins like fibronectin[7]. The biochemical events implicated in the cervical ripening are: decrease in total collagen content, increase in collagen solubility[8] and increase in collagenolytic activity. Inflammatory response[9] are involved too (Interleukins : IL1, IL8, tumor necrosis factor a, prostaglandins, nitric oxide[10]), matrix degrading enzymes (matrix metalloproteinases) and sex steroids hormones (17 b-estradiol induces ripening, estrogen stimulates collagen degradation in vitro, progesterone blocks the estrogen induced collagenolysis in vitro, progesterone receptor antagonist induces cervical ripening in the first trimester).

Sonographic findings:

Funneling of the cervix with the changes in forms T, Y, V, U[11] (correlation between the length of the cervix and the changes in the cervical internal os).



The T, Y, U, V (Trust Your Vaginal Ultrasound) stages and the bulging membranes.

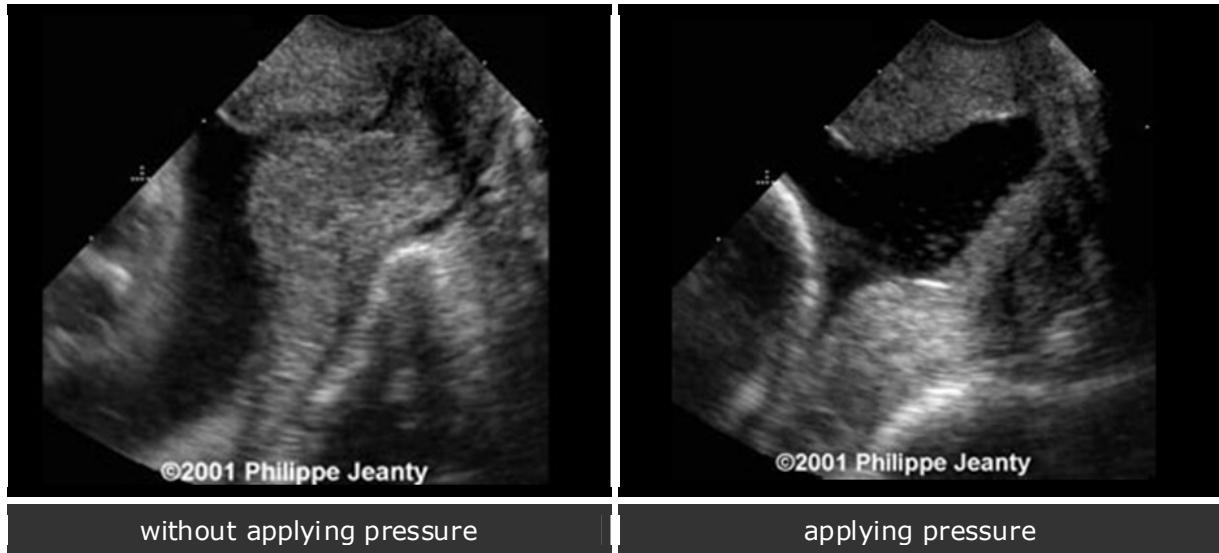


- Cervix length < 25 mm
- Protrusion of the membranes
- Presence of fetal parts in the cervix or vagina

Implications for targeted examinations: Extended exam for 15-20 minutes visualizing the cervix shows spontaneous changes of the cervix[12]. Cervical stress test at 15-24 weeks (increasing transfundal intrauterine pressure while monitoring cervical length and the appearance of funneling[13]) is recommended for the patients with:

- history of painless dilatation followed by fetal expulsion in the second trimester
- conization
- uterine malformations (uterus unicornis, uterus bicornis, uterus didelphys)
- cervical trauma (conization)
- history of spontaneous and therapeutic abortions
- preterm birth before 32 weeks .

2 images of the same cervix, 20 seconds apart, without and with applying pressure



Ultrasonography is the principal modality of the diagnosis during pregnancy (transabdominal, transperineal or transvaginal), MRI appearance of the cervical incompetence may demonstrate a higher degree of soft tissue contrast than ultrasonography[14].

Differential diagnosis: Other causes of preterm labor (PROM, chorioamnionitis , uterine contractility)

Management: In patients at risk for pregnancy loss, placement of cervical cerclages in response to sonographic detected shortening of the endocervical canal length is an acceptable alternative to the use of elective cerclage[15].

Screening for Preterm Delivery

- Mesurment of the cervical lenght

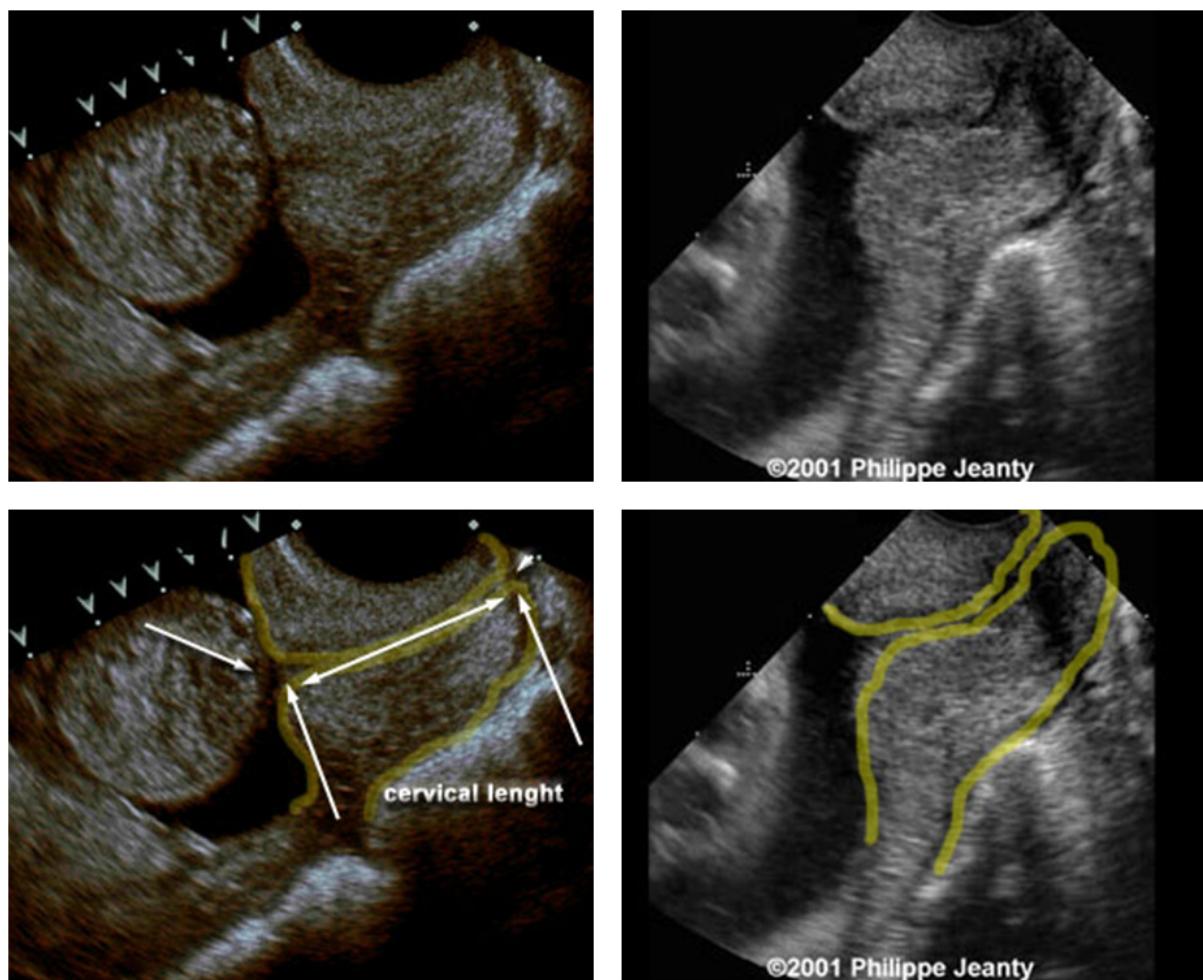
Routine ultrasound scans

11-14 weeks

- viability, number & size
- Nucal Trnslucency
- Anomalies or markers
- cervical lengh

22-24 weeks

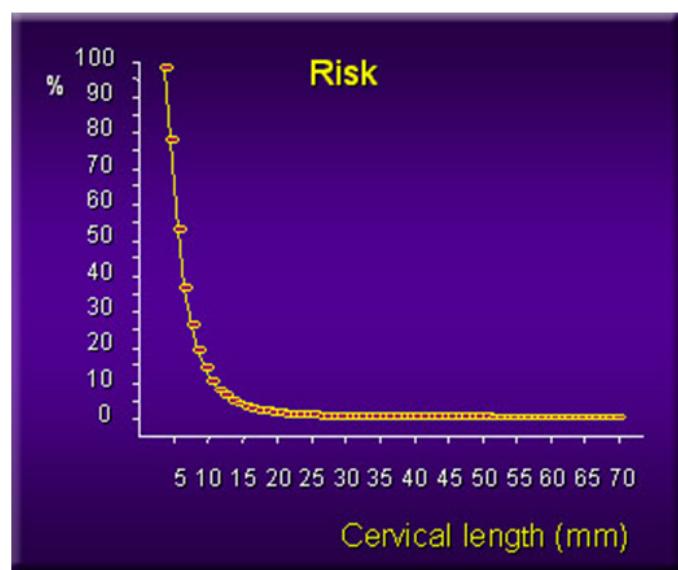
- fetal growth
- fetal doppler
- anomalies and/or markers
- cervical lengh



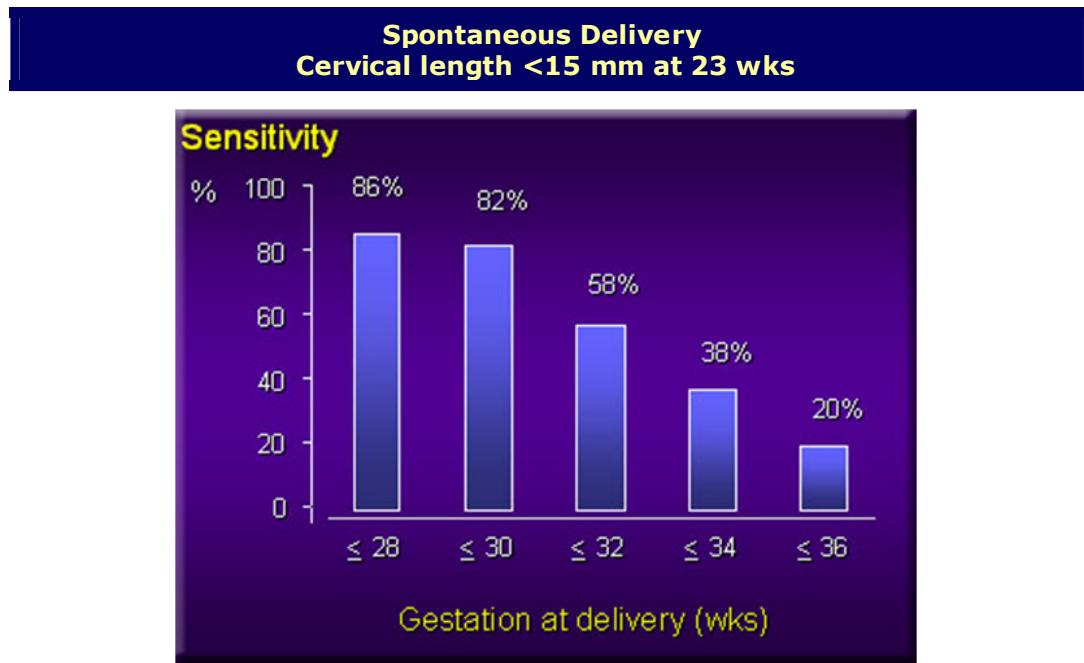
n= 1,252

Cx	LR
5 mm	52
10 mm	9,1
15 mm	2,7
20 mm	1,2
25 mm	0,7
30 mm	0,5
40 mm	0,5
50 mm	0,4
60 mm	0,1

Rate 1,52%



Risk of preterm delivery using cervical length at 23 weeks (Heath et al 1998)



n= 1,253; Screen +ve = 1.5% (Heath et al 1998)

GROWTH RESTRICTION

In singleton pregnancies, the main factors determining fetal growth are genetic potential and placental function, which is thought to be due mainly to the effectiveness of trophoblastic invasion of the maternal spiral arteries.

In monochorionic twin pregnancies, both the genetic constitution and the factors which govern trophoblastic invasion should be the same for the two fetuses. Consequently, inter-twin disparities in growth are likely to reflect the degree of unequal splitting of the initial single cell mass or the magnitude of imbalance in the bidirectional flow of fetal blood through placental vascular communications between the two circulations. In contrast, since about 90% of dichorionic pregnancies are dizygotic, inter-twin disparities in size would be due to differences in genetic constitution of the fetuses and their placentas.

In twin pregnancies, the risk of delivering growth-restricted babies is about 10 times higher than in singleton pregnancies²¹. In a study of 467 twin pregnancies in which chorionicity was assessed at the 11–14-week scan, the chance of growth restriction (birth weight below the 5th centile for gestation in singletons) of at least one of the fetuses was 34% for monochorionic and 23% for dichorionic twins²⁰. Furthermore, the chance of growth restriction of both twins was about four times as high in monochorionic (7.5%) compared to dichorionic (1.7%) pregnancies ([Figure 7](#))²⁰.

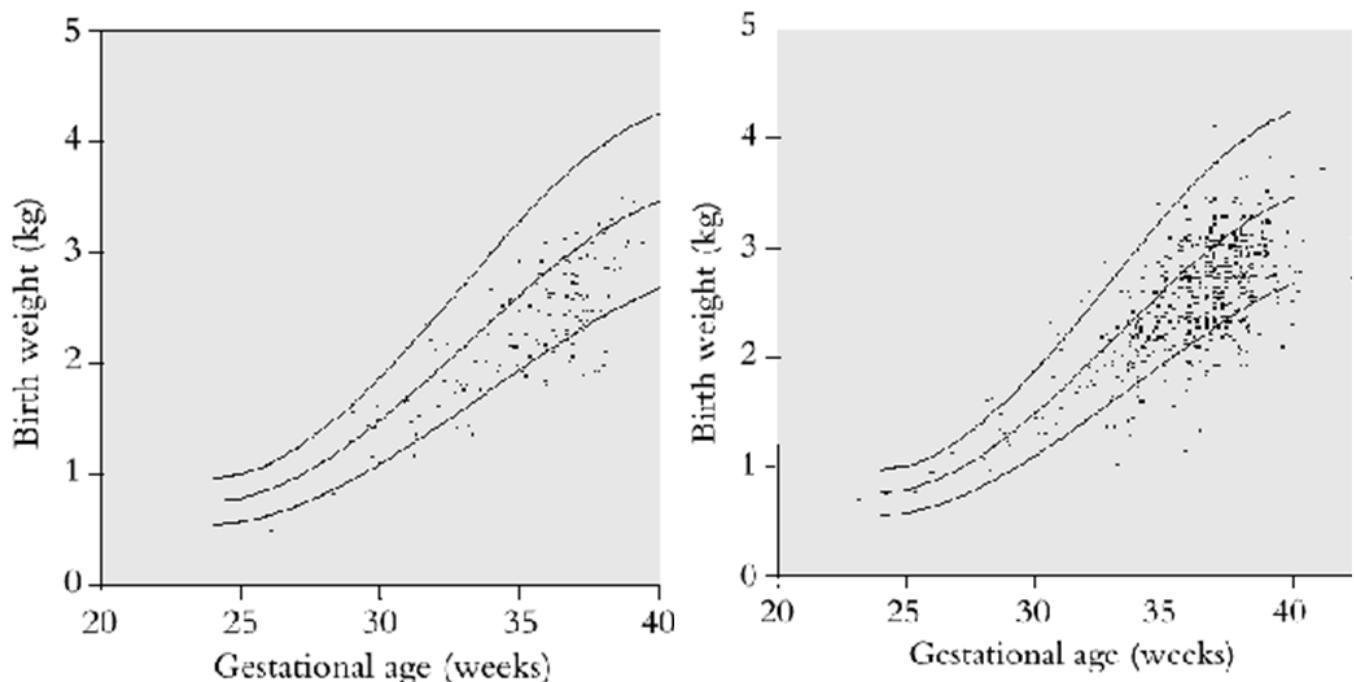


Figure 7 - The chance of growth restriction (birth weight below the 5th centile for gestation in singletons) of both twins is about four times as high in monochorionic (left) compared to dichorionic (right) pregnancies²⁰

Ultrasonographic studies in the first trimester have examined inter-twin disparities in crown-rump length to determine if this measurement is useful in the prediction of pregnancy outcome. One study examined 180 pregnancies at less than 8 weeks of gestation (median crown-rump length of 8.4 mm) and reported that in those pregnancies resulting in two live births, the median inter-twin disparity in crown-rump length was about 10% (0.9 mm); a difference of more than 3 mm was associated with a 50% chance of intrauterine death of the smaller twin²². There are also three studies reporting on a total of seven pregnancies discordant for growth restriction or congenital abnormalities that demonstrated large inter-twin disparities in crown-rump length at 6–11 weeks of gestation^{23–25}.

In a study of 123 monochorionic and 416 dichorionic twin pregnancies, there were no significant differences in inter-twin disparity in crown-rump length at the 11–14-week scan or birth weight between monochorionic and dichorionic twins ([Figure 8](#))²⁶. In addition, there was no significant correlation between inter-twin disparities in crown-rump length and inter-twin disparities in birth weight. In dichorionic pregnancies with chromosomally abnormal fetuses, and in those which ended in miscarriage or intrauterine death of one or both fetuses, the inter-twin disparity in crown-rump length was significantly higher than in pregnancies resulting in two live births. However, in the monochorionic twins with adverse pregnancy outcome, there was no significant difference in inter-twin disparity in crown-rump length from pregnancies resulting in two live births²⁶.

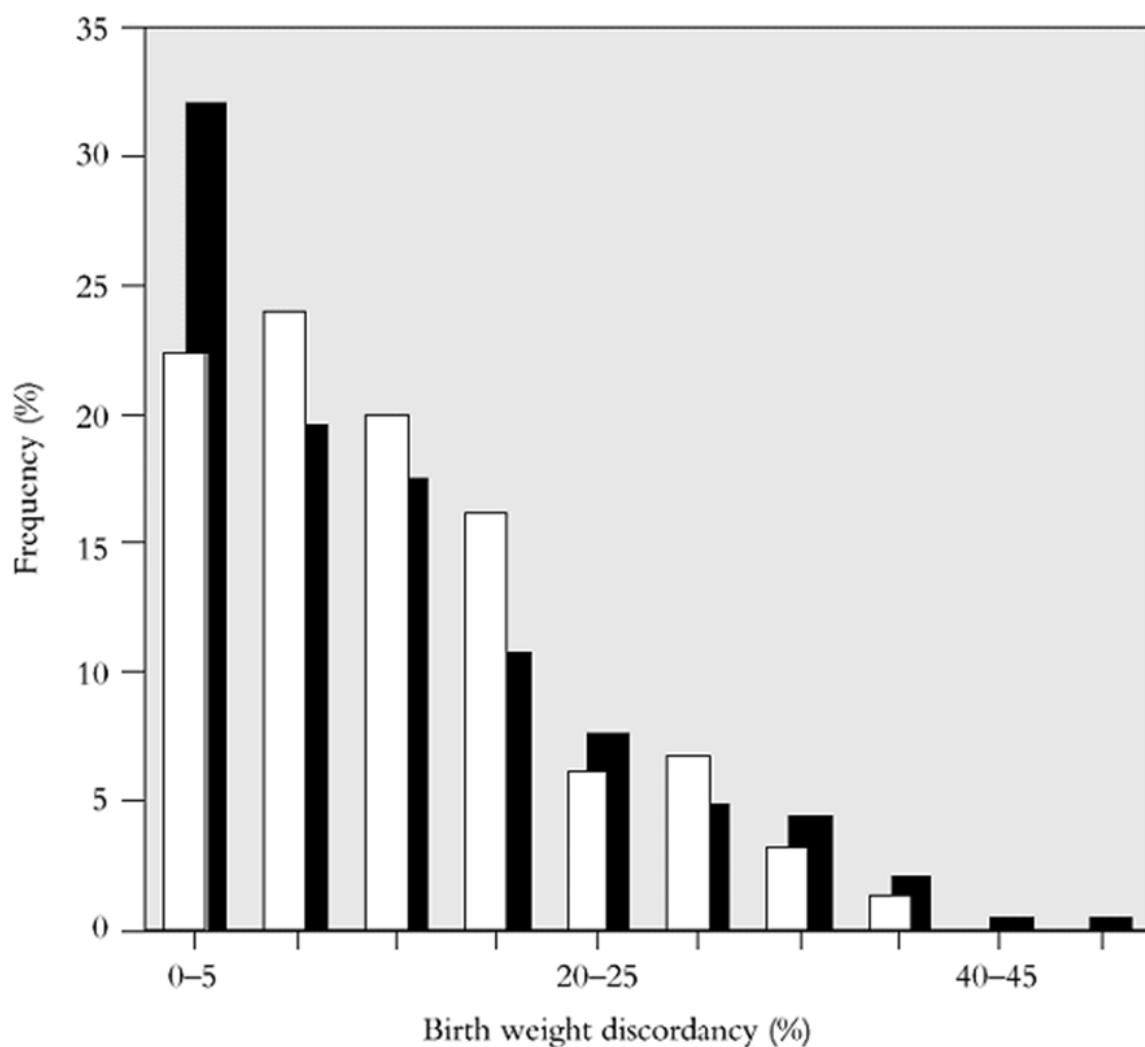


Figure 8 - There is no significant inter-twin disparity in birth weight between monochorionic (solid bars) and dichorionic (open bars) twins²⁶.

In twin pregnancies resulting in live births the median inter-twin disparity in fetal size increases with gestation from about 3% at 12 weeks to 10% at birth²⁶. In monochorionic twins, this increasing disparity may be a consequence of the degree of imbalance in fetal nutrition as a result of chronic twin-to-twin transfusion syndrome. Similarly, in dichorionic twins, the increasing disparity in size may also be due to differences in fetal nutrition, but in this case such differences may be a consequence of discordancy in the effectiveness of trophoblastic invasion of the maternal spiral arteries and therefore placental function. The finding, of no significant association between inter-twin disparity in crown-rump length and inter-twin disparity in birth weight²⁶, suggests that assessment in early pregnancy cannot provide useful prediction of the subsequent development of either mild chronic twin-to-twin transfusion syndrome in monochorionic twins or growth restriction in dichorionic twins.

The findings in dichorionic twins (that adverse pregnancy outcome or chromosomal abnormalities are associated with large inter-twin disparities in crown-rump length)²⁶, suggest that, in such pregnancies, there is early-onset growth restriction in one of the fetuses, either due to a genetic defect or impaired placentation. In addition, the association between large inter-twin disparities in crown-rump length and miscarriage are compatible with observations that, in multiple pregnancies, spontaneous or iatrogenic death of one of the fetuses can destabilize the whole pregnancy, resulting in miscarriage or severe preterm delivery.

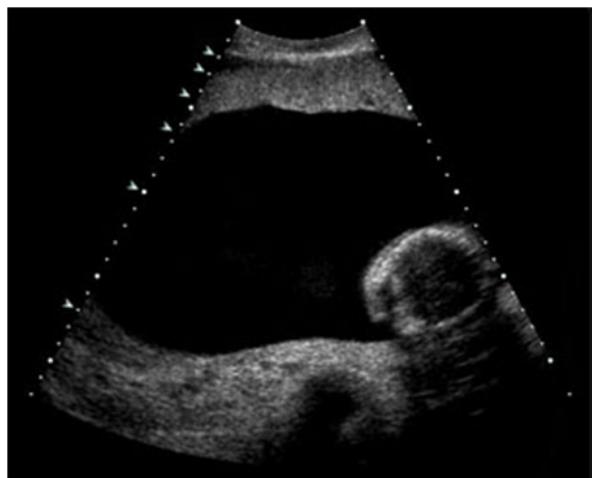
The finding in monochorionic twins, that adverse pregnancy outcome is not associated with large inter-twin disparities in crown-rump length at the 11–14-week scan, suggests that, at this early gestation, fetal growth may not be affected by impaired nutrition through such conditions as chronic fetal hemorrhage. It is possible that at this stage there is programmed fetal growth that may only be affected by serious genetic abnormalities, such as chromosomal defects, or extreme degrees of placental impairment that will subsequently result in fetal death.

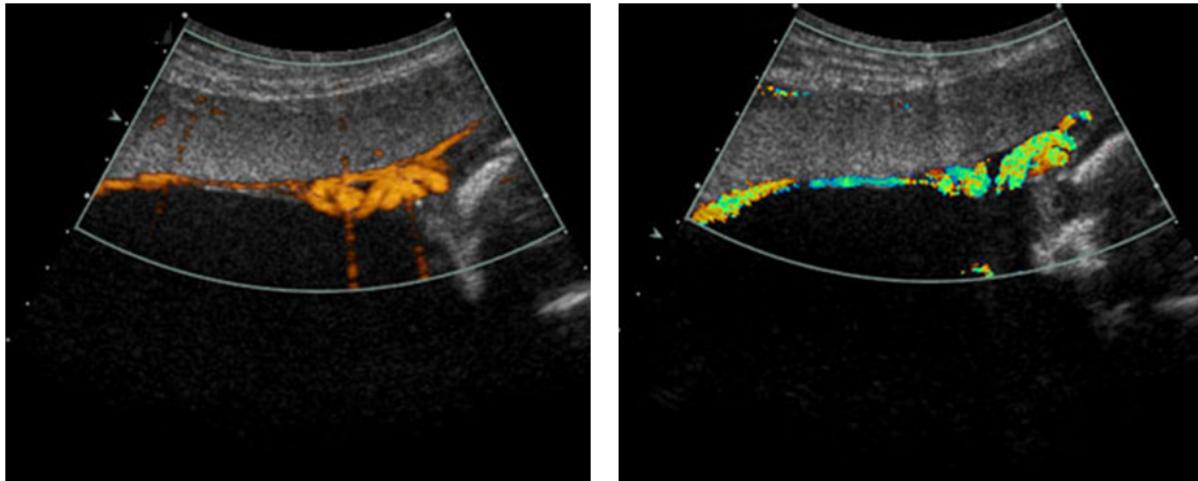
TWIN-TO-TWIN TRANSFUSION SYNDROME

In monochorionic twin pregnancies, there are placental vascular anastomoses which allow communication of the two fetoplacental circulations; these anastomoses may be arterio-arterial, veno-venous, or arterio-venous in nature²⁷. This phenomenon of a shared circulation between monochorionic twins was first described by Schatz in 1882²⁸. Anatomical studies demonstrated that arterio-venous anastomoses are deep in the placenta but almost always proceed through the cotyledonary capillary bed²⁹. In about 25% of monochorionic twin pregnancies, imbalance in the net flow of blood across the placental vascular arterio-venous communications from one fetus, the donor, to the other, the recipient, results in twin-to-twin transfusion syndrome; in about half of these cases, there is severe twin-to-twin transfusion syndrome presenting as acute polyhydramnios in the second trimester ([Figure 9](#)).



Figure 9 - Severe twin-to-twin transfusion syndrome at 20 weeks of gestation. In the polyuric recipient, there is a large bladder and polyhydramnios (left) and the anuric donor is held fixed to the placenta by the collapsed membranes of the anhydramniotic sac (right)





The precise underlying mechanism by which a select population of those mono chorionic pregnancies with vascular communications go on to develop twin-to-twin transfusion syndrome is not fully understood. However, it has been hypothesized that primary maldevelopment of the placenta of the donor twin may cause increased peripheral resistance in the placental circulation which promotes shunting of blood to the recipient; the donor therefore suffers from both hypovolemia due to blood loss and hypoxia due to placental insufficiency^{30,31}. The recipient fetus compensates for its expanded blood volume with polyuria³², but, since protein and cellular components remain in its circulation, the consequent increase in colloid oncotic pressure draws water from the maternal compartment across the placenta. A vicious cycle of hyper volemia, polyuria and hyperosmolality is established, leading to high-output heart failure and polyhydramnios.

Traditionally, the diagnosis of twin-to-twin transfusion syndrome was made retrospectively, in the neonatal period, on the basis of an inter-twin difference in birth weight of 20% or more and hemoglobin concentration of 5 g/dl or more^{33–35}. These observations were made in live births and therefore the criteria may only apply to relatively mild twin-to-twin transfusion syndrome, since severe cases result in miscarriage or stillbirth. Additionally, large inter-twin differences in hemoglobin and birth weight are found in some dichorionic twin pregnancies and are not pathognomonic of twin-to-twin transfusion syndrome³⁶.

Severe disease, with the development of polyhydramnios, becomes apparent at 16–24 weeks of pregnancy. The pathognomonic features of severe twin-to-twin transfusion syndrome by ultrasonographic examination are the presence of a large bladder in the polyuric recipient fetus in the polyhydramniotic sac, and 'absent' bladder in the anuric donor which is found to be 'stuck' and immobile at the edge of the placenta or the uterine wall, where it is held fixed by the collapsed membranes of the anhydramniotic sac (Figure 9). Other sonographic findings that may prove to be of prognostic significance include the presence of a hypertrophic, dilated and dyskinetic heart, with absence or reversal of flow in the ductus venosus during atrial contraction³⁷. In the donor, the heart may be dilated, the bowel is hyperechogenic, and there is absent end-diastolic flow in the umbilical artery; these features are commonly seen in hypoxic fetuses in pregnancies with severe uteroplacental insufficiency. Once the oligohydramnios/polyhydramnios sequence is present, the rate of death of both fetuses is about 90%³¹.

Early prediction of twin-to-twin transfusion syndrome

Ultrasonographic features of the underlying hemodynamic changes in severe twin-to-twin transfusion syndrome may be present from as early as 11–14 weeks of gestation and manifest as increased nuchal translucency thickness in one or both of the fetuses. In a study of 132 monochorionic twin pregnancies, including 16 that developed severe twin-to-twin transfusion syndrome at 15–22 weeks of gestation, increased nuchal translucency (above the 95th centile of the normal range) at the 11–14-week scan was associated with a four-fold increase in risk for the subsequent development of severe twin-to-twin transfusion syndrome (Figure 10)³⁸. Intertwin discrepancies in crown-rump length were not predictive of subsequent development of twin-to-twin transfusion syndrome. It is possible that increased nuchal translucency thickness in the recipient fetus may be a manifestation of heart failure due to

hypervolemic congestion. With advancing gestation and the development of diuresis that would tend to correct the hypervolemia and reduce heart strain, both the congestive heart failure and nuchal translucency resolve.

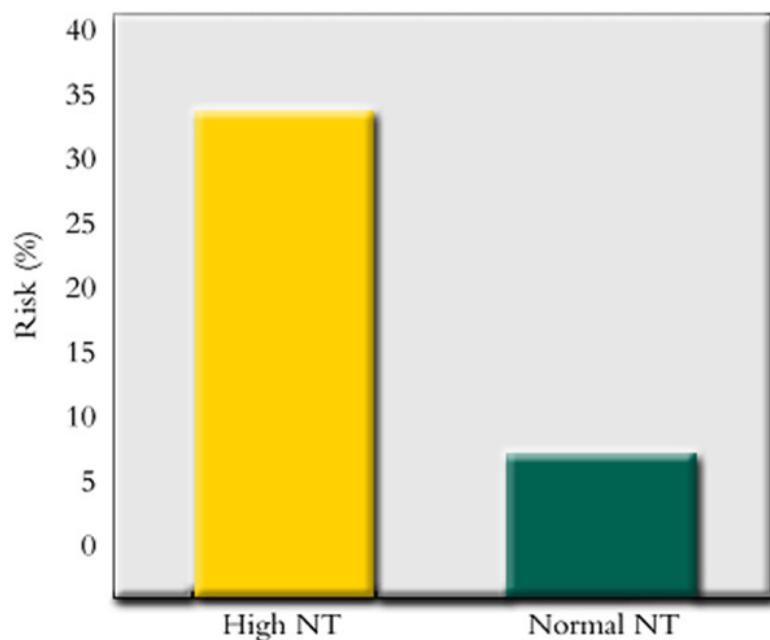


Figure 10 - In monochorionic twin pregnancies at the 11–14-week scan, increased nuchal translucency (NT) thickness in one or both fetuses is associated with a four-fold increase in risk for the subsequent development of severe twin-to-twin transfusion syndrome³⁸

In fetuses of monochorionic twin pregnancies, the prevalence of increased nuchal translucency thickness is higher than in dichorionic twins (see section below), presumably because of the circulatory imbalance associated with twin-to-twin trans fusion syndrome. Consequently, the presence of increased nuchal translucency thickness in monochorionic twins at 11–14 weeks should stimulate the sonographer to undertake close surveillance for early diagnosis of the clinical features of severe twin-to-twin transfusion syndrome. The extent to which such an earlier diagnosis would lead to therapeutic interventions with a higher survival rate remains to be determined.

An early manifestation of disparity in amniotic fluid volume due to twin-to-twin transfusion syndrome is inter-twin membrane folding, because of the oliguria and collapsed amniotic sac of the donor twin ([Figure 11](#))³⁹. In about one-quarter of monochorionic twin pregnancies at 15–17 weeks of gestation, there is membrane folding, and in about half of such cases there is progression to the polyhydramnios/anhydramnios sequence of severe twin-to-twin transfusion syndrome; in the other half, there is moderate twin-to-twin transfusion syndrome with large discrepancies in amniotic fluid volume and fetal size persisting throughout pregnancy. In about 75% of monochorionic twins, there is no membrane fold and these pregnancies are not at increased risk for miscarriage or perinatal death³⁹.

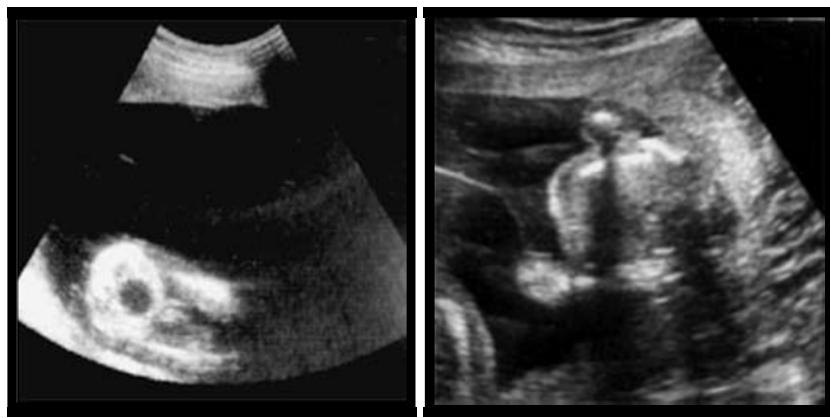


Figure 11 - Monochorionic twin pregnancies at 16 weeks of gestation affected by early twin-to-twin transfusion syndrome, showing folding of the inter-twin membrane pointing towards the recipient amniotic sac and the increased echogenicity of the amniotic fluid in the donor sac (left) and folding of the inter-twin membrane around the limb of the donor fetus (right)

In severe twin-to-twin transfusion syndrome presenting with acute polyhydramnios at 16–24 weeks of gestation, survival with expectant management is less than 10%³¹. Improved survival of such pregnancies has been reported after treatment with serial amniocenteses and drainage of large volumes of amniotic fluid; this treatment presumably prevents the polyhydramnios-mediated risk of spontaneous abortion or very premature delivery. In studies published before 1991, amniodrainage was associated with survival in 40–50% of the cases³¹. However, more recent papers have reported survivals of 70–80% of fetuses^{40–42}.

It is possible that the apparent marked improvement in survival with serial amnio drainage, compared to previous studies that used the same treatment protocols, could, at least in part, be the consequence of the inclusion of pregnancies with moderate twin-to-twin transfusion syndrome. Thus, the widespread use of routine ultrasound examination and the identification of monochorionic pregnancies with large inter-twin disparities in size and amniotic fluid volume could have stimulated obstetricians to undertake amniodrainage in pregnancies with moderate twin-to-twin transfusion syndrome that would have resulted in live births even without such treatment. Since in only about 50% of pregnancies with twin-to-twin transfusion syndrome is the condition severe (where amniodrainage may truly be associated with a survival of about 40–50%), the inclusion of pregnancies with moderate twin-to-twin transfusion syndrome (where survival even with expectant management may be as high as 100%) could account for the apparent recent improvement in survival with amniodrainage from about 40–50% to 70–80%.

MONOAMNIOTIC TWINS

Splitting of the embryonic mass after day 9 of fertilization results in monoamniotic twins. In these cases, there is a single amniotic cavity with a single placenta and the two umbilical cords insert close to each other. Monoamniotic twins are found in about 1% of all twins or about 5% of monochorionic twins. In a series of 1288 twin pregnancies (including 317 monochorionic) examined at the 11–14-week scan at the Harris Birthright Research Centre, King's College Hospital, there were 14 mono amniotic pregnancies (including four with conjoined twins and two with twin reversed arterial perfusion sequence).

In monoamniotic twins, the fetal loss rate is about 50–75%, due to fetal malformations, preterm delivery and complications arising from the close proximity of the two umbilical cords. Cord entanglement is generally thought to be the underlying mechanism for the majority of fetal losses, and attempts have been made to prevent this complication by the administration to the mother of sulindac

during the second trimester to stabilize the fetal lie by reducing the amniotic fluid volume⁴³. However, cord entanglement is found in most cases of monoamniotic twins and this is usually present from the first trimester of pregnancy⁴⁴⁻⁴⁶. Therefore, a more likely cause of fetal death in monoamniotic twins, which occurs suddenly and unpredictably, is acute twin-to-twin transfusion syndrome. The close insertion of the umbilical cords into the placenta is associated with large-caliber anastomoses between the two fetal circulations^{46,47}. Consequently, an imbalance in the two circulations could not be sustained for prolonged periods of time (which is necessary for the development of the classic features of twin-to-twin transfusion syndrome), but would rather have major hemodynamic effects, causing sudden fetal death.

On the basis of existing data, the diagnosis of monoamniotic twins at the 11–14- week scan should lead to counselling of the parents as to the high risk of sudden, unexpected and non-preventable fetal death. In our series of eight monoamniotic pregnancies with two separate fetuses diagnosed by the early scan, there were four discordant for major fetal abnormality and these resulted in termination of pregnancy or death of both fetuses. In the four cases where both fetuses were normal, one resulted in survival of both twins, another in survival of one twin and two in intrauterine death of both fetuses ([Table 1](#)).

Table 1 - Pregnancy outcome and management in eight monoamniotic pregnancies diagnosed at 10–13 weeks of gestation at the Harris Birthright Research Centre.

Gestation (weeks)	NT (mm)	Findings	Management	Outcome
13	1,2/1,2	anencephaly/normal	termination	
11	5,5/1,8	body stalk anomaly/normal	termination	
11	4,4/2,0	kyphoscoliosis/normal	termination	
13	6,0/2,0	diaphragmatic hernia/normal	expectant	IUD/IUD at 21 weeks
10	1,7/1,2	normal/normal	expectant	alive at 31 weeks
11	1,1/1,0	normal/normal	expectant	IUD/IUD at 21 weeks
12	2,1/2,1	normal/normal	sulindac	IUD/IUD at 31 weeks
12	1,5/1,5	normal/normal	sulindac	IUD 30 weeks/alive 34 weeks

NT, nucal translucency; IUD, intra-uterine death

First trimester diagnosis of monoamniotic twin pregnancies - Sebire et al 2000

Ultrasound findings and pregnancy outcome in eight nonconjoined monoamniotic twinn pregnancies at 11-14 weeks gestation

Case	Gestation	Ultrasound findings		Outcome	
		Twin 1	Twin 2	Twin 1	Twin 2
1	13 weeks	CRL 42 mm NT 2,0 mm	CRL 38 mm, NT 4,4 mm Kyphoscoliosis	IUD	TOP 13 weeks
2	13 weeks	CRL 66 mm, NT 1,2 mm Anencephaly	CRL 79mm, NT 1,2 mm	TOP 13 weeks	TOP 13 weeks
3	11 weeks	CRL 48 mm, NT 1,8 mm	CRL 55mm, NT 5,5 mm, body stalk anomaly	LB 34 weeks	NNND 34 weeks
4	13 weeks	CRL 63 mm, NT 6,0mm Diaphragmatic hernia	CRL 66 mm, NT 2,0 mm	IUD 21 weeks	IUD 21 weeks
5	12 weeks	CRL 52 mm, NT 1,1 mm	CRL 53 mm, NT 1,0 mm	LB 31 weeks	LB 31 weeks
6	10 weeks	CRL 38 mm, NT 1,2 mm	CRL 39 mm, NT 1,7 mm	IUD 30 weeks	LB 31 weeks
7	12 weeks *	CRL 59 mm, NT 1,5 mm	CRL 58 mm, NT 1,5 mm	IUD 30 weeks	IUD 30 weeks
8	12 weeks **	CRL 61 mm, NT 2,1 mm	CRL 67 mm, NT 2,1 mm	IUD 31 weeks	IUD 31 weeks

* Sulindac treatment from 23 weeks; ** Sulindac treatment from 20 weeks . CRL, crown-rump-length; NT, nucal translucency thickness; IUD, Intra-uterine death; TOP, termination of pregnancy; LB, livebirth; NND, neonatal death

Conjoined twins

Splitting of the embryonic mass after day 12 of fertilization results in conjoined twins, which are found in about 1% of monochorionic pregnancies. Conjoined twins are classified, according to the dominant site of interfetal body part connection, into five major types: thoracopagus (thorax, 30–40%), omphalopagus (abdomen, 25–30%), pygopagus (sacrum, 10–20%), ischiopagus (pelvis 6–20%) and craniopagus (head, 2–16%). The prognosis depends on the site and extent of conjoining, but, in general, about 50% are stillborn and one-third of those born alive have severe defects for which surgery is not possible. In the live-born cases in whom planned surgery is carried out, about 60% of infants survive^{48,49}.

In our four cases of conjoined twins diagnosed at the 11–14-week scan, the nuchal translucency was increased in six of the eight fetuses (0.5 mm and 6.5 mm at 11 weeks, 4.2 mm and 7.5 mm at 11 weeks, 2.4 mm and 3.6 mm at 13 weeks and 3.5 mm and 7.0 mm at 13 weeks, respectively). However, the extent to which nuchal translucency provides useful prediction as to the outcome of such pregnancies is uncertain. In cases diagnosed in the first trimester, the patients usually elect termination of pregnancy. There are no series reporting on the natural history of the condition.

*First trimester diagnosis of monoamniotic twin pregnancies - Sebire et al
2000*

Ultrasound findings in four conjoined monoamniotic twin pregnancies at 11–14 weeks of gestation

Case	Gestation	Ultrasound findings
1	13 weeks	CRL 58 mm, NT 7,0mm and CRL 60 mm, NT 3,5mm, thoraco-omphalopagous
2	11 weeks	CRL 50mm, NT 4,2mm and CRL 49mm, NT 7,5mm, thoracopagus
3	13 weeks	CRL 77mm, NT 2,4mm and CRL 75mm, NT 3,6mm, thoraco-omphalopagous
4	11 weeks	CRL 55mm, NT 6,5mm and CRL 56mm, NT 0,5mm, thoracopagus

CRL, crown-rump-length; NT, nuchal translucency thickness

Classification:

Conjoined twins are classified according to the area of the bodies where the fusion takes place and the involvement of internal organs. The symmetrical and equal forms, in which the twins have equal or nearly equal duplication of structures, are called *duplicata completa*. When there is an unequal duplication of structures they are called *duplicata incompleta*, and this category includes the most severe types of conjoined twins in which just few organs systems are duplicated. The most frequent varieties of conjoined twins are thoracopagus (40-74%), omphalopagus (10-33%), pygopagus (18%), ischiopagus (6%) and craniopagus (1-6%). The classification of conjoined twins is described in the table.

Duplicata incompleta: duplication occurring in only one part or region of the body.

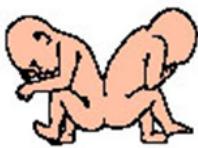


Examples:

- Diprosopus:** one body, one head, two faces.
- Dicephalus:** one body, two heads
- Dipygus:** one head, thorax and abdomen with two pelvis, and/or external genitalia.

Duplicata completa: two complete conjoined twins.

Terata catadidyma: conjunction in the lower part of the body.



Examples:

Ischiopagus: joined by inferior portion of coccyx and sacrum

Pygopagus: joined by lateral and posterior portion of coccyx and sacrum

Terata anadidyma: conjunction in the upper part of the body



Examples:

Syncephalus: joined by the face

Craniopagus: joined at homologous portion of the cranial vault

Terata anacatadidyma: conjunction in the midpart of the body



Examples:

Thoracopagus: joined at the thoracic wall

Xiphopagus: joined at xiphoid process

Omphalopagus: joined in the area between the xiphoid cartilage and the umbilicus

Rachipagus: joined at the level of the spines above the sacrum

Adapted from: Romero, R., Pilu, G., Jeanty, P., Ghidini, A. and Hobbins, J.C.(1988). Prenatal Diagnosis of Congenital Anomalies , p 405. (courtesy from Philippe Jeanty - www.thefetus.net/)

In one attempt to universalize the current nomenclature, a new classification was proposed recently based on the theoretical site of union:

Ventral union: twins united along the ventral aspect.

Cephalopagus: fused from the top of the head down to the umbilicus. Two rudimentary (fused) faces, four arms and four legs. Lower abdomen and pelvis are separated. The cephalothoracopagus Janiceps type is a rare variety of conjoined twins in which the fetuses are joined face to face, the face of each fetus being split in the midline and in half turned outward, so that each observed face is made up of the right face of one fetus and the left face of the other. The name originates from Janus, in Roman mythology, the god of gates and doorways, his statue with two faces, facing east and west for the beginning and ending of the day; and caput, head.

Thoracopagus: united face-to-face from the upper thorax down to the umbilicus, with heart involvement always. Four arms, four legs, two pelvises.

Omphalopagus: joined face-to-face primarily in the area of the umbilicus, and sometimes involving the lower thorax, but always preserving two distinct hearts. There is not even a cardiac vessel in common. Two pelvis, four arms and four legs.

Ischiopagus: united ventrally from the umbilicus to a large conjoined pelvis with two sacrum and two symphyses pubis. They appear more frequently joined end-to-end with the spine in a straight line, but they can also present face-to-face with a joined abdomen. Four arms, four legs, and in general, a single external genitalia and a single anus.

Lateral union: twins joined side-by-side with shared umbilicus, abdomen, and pelvis.

Parapagus: twins that share a conjoined pelvis, one symphysis pubis and one or two sacrums. When the union is limited to the abdomen and pelvis (does not involve the thorax) it is called dithoracic parapagus. If there is one trunk with two heads it is called dicephalic parapagus. If there is a single trunk and a single head with two faces they are diprosopic parapagus. Two, three or four arms, and two or three legs.

Dorsal union: twins joined at the dorsal aspect of the primitive embryonic disc. There is no involvement of thorax and abdomen

Craniopagus: united on any portion of the skull, except the face or foramen magnum. They share bones of the cranium, meninges, and occasionally brain surface. Two trunks, four arms and four legs.

Pygopagous: they share dorsally the sacrococcygeal, perineal regions and occasionally the spinal cord. There is one anus, two rectums, four arms and four legs.

Rachipagus: twins fused dorsally above the sacrum, involving different segments of the column. This type is extremely rare.

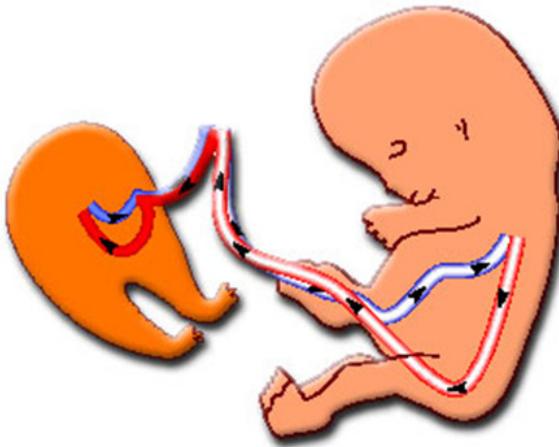
Twin reversed arterial perfusion sequence (TRAP)

The most extreme manifestation of twin-to-twin transfusion syndrome, found in approximately 1% of monochorionic twin pregnancies, is acardiac twinning (acardius chorioangiopagus parasiticus). This twin disorder has been named 'twin reversed arterial perfusion' (TRAP) sequence because the underlying mechanism is thought to be disruption of normal vascular perfusion and development of one twin (the recipient) due to an umbilical arterio–arterio anastomosis with the other (donor or pump) twin⁵⁰. At least 50% of donor twins die due to congestive heart failure or severe preterm delivery, the consequence of polyhydramnios^{50,51}. All perfused twins die due to the associated multiple malformations.

Prenatal treatment is by occlusion of the blood flow to the acardiac twin by endoscopic ligation or laser coagulation of the umbilical cord^{52,53}. A less invasive technique is ultrasound-guided laser coagulation of the umbilical cord vessels within the abdomen of the acardiac twin, which is carried out at about 16 weeks of gestation.



Two sets of acardiac twins demonstrate the range of development (or absence of development) of the cephalic end. (www.thefetus.net)



In the twin-reversed arterial perfusion syndrome the "acardiac" twin is perfused retrogradely with poorly oxygenated blood that should have gone to the placenta.

Management

The management includes conservative and invasive therapies. Conservative management includes serial cardiotocography (CTG), ultrasonography and echocardiography, and opportune delivery. Non-invasive therapies may be used supporting the cardiac function of the pump twin with digoxin and indomethacin. The more invasive management consists in termination of pregnancy or interruption of flow to the acardiac fetus, by surgical extraction (hysterotomy with selective delivery of the acardiac twin) and ligation of the acardiac twin's umbilical cord ^{1,2} ultrasound-guided embolization of the cardiac twin's umbilical artery with absolute alcohol^{3,4}, platinum coils or thrombogenic coils, laser vaporization ^{4,5}. Large numbers are not available to compare the various techniques.

Recommended Literature - Management

- 1 - Willcourt RJ, Naughton MJ, Knutzen VK, Fitzpatrick C. Laparoscopic ligation of the umbilical cord of an acardiac fetus. *J Am Assoc Gynecol Laparosc* 1995 May;2(3):319-21.
- 2 - Quintero R, Munoz H, Hasbun J, Pommer R, Gutierrez J, Sanchez J, Hidalgo G, Caerstens E, Munoz L, Ramirez R. Fetal endoscopic surgery in a case of twin pregnancy complicated by reversed arterial perfusion sequence. *Rev Chil Obstet Ginecol* 1995;60(2):112-6.
- 3 - Sepulveda W, Bower S, Hassan J, Fisk NM. Ablation of acardiac twin by alcohol injection into the intraabdominal umbilical artery. *Obstet Gynecol* 1995 Oct;86(4):680-1.
- 4 - Hecher K, Reinhold U, Gbur K, Hackeloer BJ. Interruption of umbilical blood flow in an acardiac twin by endoscopic laser coagulation. *Geburtshilfe Frauenheilkd* 1996 Feb;56(2):97-100.
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DEATH OF ONE FETUS IN TWIN PREGNANCY

Intrauterine death of a fetus in a twin pregnancy may be associated with adverse outcome for the co-twin, but the type and degree of risk are dependent on the chorionicity of the pregnancy.

Missed abortions in twin pregnancies in the first trimester

In singleton pregnancies at the 11–14-week scan, the prevalence of missed abortion is about 2%⁵⁴. In a study of 492 twin pregnancies, the prevalence of death of one or both of the fetuses at the early scan was 5%; additionally, in 24% of pregnancies with one fetal death, there was a subsequent death of the co-twin or miscarriage⁵⁵. In twin pregnancies with two live fetuses at 10–14 weeks, the overall risk of subsequent miscarriage is about 5% (2% for dichorionic and 12% for monochorionic pregnancies). Therefore, the prevalence of missed abortion at the 11–14-week scan in twin pregnancies is about twice as high as in singletons and the risk of subsequent miscarriage in twins with one missed abortion is about five times as high as in normal twins.

Intrauterine death of one fetus in the second or third trimester

Death of one fetus in dichorionic pregnancies carries a risk to the remaining fetus, mainly due to preterm delivery, which may be the consequence of release of cytokines and prostaglandins by the resorbing dead placenta. In dichorionic twins, the risk of death or handicap of the co-twin in such cases is about 5–10%, whereas, in mono chorionic twins, there is at least a 25% risk of death or neurological handicap due to hypotensive episodes in addition to the risk of preterm delivery⁵⁶. The acute hypotensive episode is the result of hemorrhage from the live fetus into the dead fetoplacental unit^{57,58}. In singleton pregnancies, death and retention of the fetus may be associated with maternal disseminated intravascular coagulation; however, in twin pregnancies with one dead fetus, this complication has only rarely been reported.

STRUCTURAL DEFECTS IN MULTIPLE PREGNANCY

Fetal structural defects in twin pregnancies can be grouped into those which also occur in singletons and those specific to the twinning process, the latter being unique to monozygotic twins. For any given defect, the pregnancy may be concordant or discordant in terms of both the presence or type of abnormality and its severity. There is no increased risk of congenital abnormalities in pregnancies from assisted reproduction compared to those achieved spontaneously⁵⁹.

Discordancies in dizygotic twins are usually due to differences in genetic predisposition. In monozygotic pregnancies discordancies may be:

1. The consequence of variation in gene expression (secondary to postzygotic mutation, parenteral imprinting effects or asymmetric X-inactivation);
2. Asymmetric splitting of the cell mass, in either volume or cytoplasmic content, resulting in unequal potential for development (the 'Christmas cracker' hypothesis);
3. Splitting after laterality gradients are determined, resulting in malformations of laterality, such as cardiac and mid-line defects; or
4. Hemodynamic factors in monochorionic pregnancies resulting in abnormal flow patterns, and thence in cardiac defects or the twin reversed arterial perfusion sequence.

The prevalence of structural defects per fetus in dizygotic twins is the same as in singletons, whereas the rate in monozygotic twins is 2–3 times higher^{60,61}. Concordance of defects (both fetuses being affected) is uncommon, being found in about 10% of dichorionic and 20% of monochorionic pregnancies.

Management of pregnancies discordant for structural defects

Multiple pregnancies discordant for a fetal abnormality can essentially be managed expectantly or by selective fetocide of the abnormal twin. In cases where the abnormality is non-lethal but may well result in serious handicap, the parents need to decide whether the potential burden of a handicapped child is enough to risk loss of the normal twin from fetocide-related complications. In cases where the abnormality is lethal, it may be best to avoid such risk to the normal fetus, unless the condition itself threatens the survival of the normal twin.

This management dilemma is exemplified by pregnancies discordant for anencephaly, which is always lethal but may be associated with the development of polyhydramnios, which places the normal co-twin at risk of neonatal death from severe preterm delivery.

A study of 24 twin pregnancies discordant for anencephaly reported that 13 were dichorionic and 11 monochorionic⁶². In the dichorionic group, five pregnancies had selective fetocide at 17–21 weeks; one pregnancy resulted in spontaneous abortion but, in the others, a healthy baby was delivered at a median gestation of 37 weeks. The other six dichorionic pregnancies were managed expectantly but four developed polyhydramnios at 26–30 weeks; in one case amniodrainage and in another selective fetocide were carried out. In this group, the median gestation at delivery was 35 weeks. The 11 monochorionic pregnancies were managed expectantly and, in three, there was intrauterine death of both fetuses. In the other eight cases, the normal twin was liveborn at a median gestation of 34 weeks; in four of the pregnancies, polyhydramnios developed and two of these were managed by amniodrainage.

The main issues in the management of pregnancies discordant for anencephaly are:

1. The prevalences of monochorionicity and dichorionicity in twin pregnancies discordant for anencephaly are similar, and, by implication, the prevalence of anencephaly is much higher in monochorionic than dichorionic pregnancies. In a study of 2874 twin and 334 912 singleton pregnancies from the same population over the same period, the prevalence of anencephaly was 10.4/10 000 in twins compared to 2.8/10 000 in singletons⁶³. This increase was mainly found in like-sex compared to unlike-sex pairs and, by implication, in monozygotic compared to dizygotic pregnancies. Furthermore, the prevalence of concordancy for anencephaly in monozygotic twins is twice as high as in dizygotic pregnancies⁶⁴, and, consequently, there may be a genetic contribution to the pathogenesis of neural tube defects; however, concordancy for anencephaly is found in less than 10% of affected pregnancies and, therefore, the contribution of environmental factors may be of greater importance than that of genetic factors.
2. Anencephaly is associated with a high risk of preterm delivery before 32 weeks, which is usually due to the development of polyhydramnios secondary to reduced fetal swallowing. In a study of 60 singleton pregnancies with anencephaly, before the advent of prenatal diagnosis, the prevalence of clinical polyhydramnios was 49%⁶⁵.
3. In dichorionic twins discordant for anencephaly, the two management options are selective fetocide or serial ultrasound examinations for early diagnosis of polyhydramnios, which can then be treated either by amniodrainage or selective fetocide. Selective fetocide is associated with mortality of the normal twin through procedure-related miscarriage. The risk of miscarriage after selective fetocide is about 5% or 15% depending on whether the procedure is carried out before or after 16 weeks of gestation, respectively⁶⁶. Since first-trimester ultrasound examination is increasingly being introduced as part of routine antenatal care and anencephaly can be reliably diagnosed at 11–14 weeks of gestation⁶⁷, it is possible that the majority of twin pregnancies discordant for anencephaly will now be diagnosed sufficiently early for safer selective fetocide. An additional advantage of earlier selective fetocide is that the risk of severe preterm delivery is reduced and, on average, the gestation at delivery of the normal twin is later than with fetocide after 16 weeks⁶⁶.
4. In monochorionic twin pregnancies, selective fetocide is not possible because death of the anencephalic fetus would be followed by death of the normal co-twin; this may be due to transplacental passage of the injected potassium chloride or acute exsanguination through the vascular anastomoses into the placenta of the dead anencephalic fetus. However, since expectant management is associated with spontaneous intrauterine death of the anencephalic

fetus in about 25% of cases, this option can also result in the death of the normal twin through similar mechanisms. Future research may demonstrate that the optimal management of monochorionic twin pregnancies discordant for anencephaly is selective fetocide by occlusion of the umbilical cord vessels of the abnormal fetus.

In twin pregnancies discordant for lethal abnormalities, the aims are to maximize the chances of survival of the normal twin and prevent severe preterm delivery. Early diagnosis through routine ultrasound examination at 11–14 weeks will inevitably stimulate further research in this area. The questions to be resolved by multicenter randomized studies are whether the risk of death and severe preterm delivery are less with expectant management or selective fetocide in the first trimester. In the case of dichorionic pregnancies, fetocide can be carried out by the traditional method of intracardiac injection of potassium chloride, whereas, in monochorionic pregnancies, fetocide would necessitate occlusion of the umbilical cord vessels.

CHROMOSOMAL DEFECTS IN MULTIPLE PREGNANCY

In multiple pregnancies compared to singletons, prenatal diagnosis of chromosomal abnormalities is complicated because, first, effective methods of screening, such as maternal serum biochemistry, are not applicable; second, the techniques of invasive testing may provide uncertain results or may be associated with higher risks of miscarriage; and, third, the fetuses may be discordant for an abnormality, in which case one of the options for the subsequent management of the pregnancy is selective fetocide.

In dizygotic pregnancies, the maternal age-related risk for chromosomal abnormalities for each twin may be the same as in singleton pregnancies and, therefore, the chance that at least one fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. Furthermore, since the rate of dizygotic twinning increases with maternal age, the proportion of twin pregnancies with chromosomal defects is higher than in singleton pregnancies.

In monozygotic twins, the risk for chromosomal abnormalities is the same as in singleton pregnancies and, in the vast majority of cases, both fetuses are affected. There are, however, occasional case reports of monozygotic twins discordant for abnormalities of autosomes or sex chromosomes, most commonly with one fetus having Turner syndrome and the other either a normal male or female phenotype, but usually with a mosaic karyotype^{68–71}.

The relative proportion of spontaneous dizygotic to monozygotic twins in the United Kingdom is about 2:1 and, therefore, the prevalence of chromosomal abnormalities affecting at least one fetus in twin pregnancies would be expected to be about 1.6 times that in singletons.

Since it is now possible to determine chorionicity antenatally by ultrasonography, in counselling parents, it is possible to give more specific estimates of one and/or both fetuses being affected, depending on chorionicity. Thus, in monochorionic twins, the parents can be counselled that both fetuses would be affected and this risk is similar to that in singleton pregnancies. If the pregnancy is dichorionic, then the parents can be counselled that the risk of discordancy for a chromosomal abnormality is about twice that in singleton pregnancies, whereas the risk that both fetuses would be affected can be derived by squaring the singleton risk ratio. For example, in a 40-year-old woman with a risk for trisomy 21 of about 1 in 100 based on maternal age, in a dizygotic twin pregnancy the risk that one fetus would be affected would be 1 in 50 (1 in 100 plus 1 in 100), whereas the risk that both fetuses would be affected is 1 in 10,000 (1 in 100 x 1 in 100). This is, in reality, an oversimplification, since, unlike monochorionic pregnancies that are always monozygotic, only about 90% of dichorionic pregnancies are dizygotic.

Screening by second-trimester biochemistry

In singleton pregnancies, screening for trisomy 21 by a combination of maternal age and second-trimester maternal serum biochemistry can detect about 60% of trisomy 21 cases for a 5% false-positive rate.

In twin pregnancies, the median values for maternal serum markers, such as α -fetoprotein, hCG, free b-hCG and inhibin-A, are about twice those for singleton pregnancies⁷². When this is taken into account

in the mathematical modelling for calculation of risks, it is estimated that serum screening in twins may identify about 45% of affected fetuses for a 5% false-positive rate⁷².

Even if prospective studies demonstrate that serum testing in twins is effective, the following problems would still need to be addressed:

1. The detection rate for an acceptable low false-positive rate, especially since invasive testing in multiple pregnancies is technically more demanding;
2. In the presence of a 'screen-positive' result, there is no feature to suggest which fetus may be affected; and
3. If the pregnancy is discordant for a chromosomal defect, further management by way of selective termination carries increased risk in the second compared to the first trimester.

Screening by first-trimester biochemistry

In a prospective screening study by measurement of fetal nuchal translucency thickness, maternal serum free b-hCG was measured in 4181 singleton and 148 twin pregnancies; in the latter group, there were 12 pregnancies with trisomy 21 in either one ($n = 10$) or both ($n = 2$) fetuses⁷³. In the normal twin pregnancies, compared to singletons, the median maternal serum free b-hCG adjusted for maternal weight was 1.94 MoM. In the 12 trisomy 21 twin pregnancies, the median level of free b-hCG was significantly higher than in normal twins but the level was above the 95th centile in only one case. These results suggest that measurement of maternal serum free b-hCG is unlikely to be useful in the prediction of fetal trisomy 21 at 11–14 weeks.

Screening by fetal nuchal translucency thickness

In a screening study for trisomy 21 involving 448 twin pregnancies, nuchal translucency thickness was measured in each fetus and the risk was estimated by combining with maternal age. The nuchal translucency was above the 95th centile of the normal range (for crown–rump length in singletons) in 7.3% fetuses, including 88% of those with trisomy 21 (Table 2)⁷⁴. Increased translucency was also present in four fetuses with other chromosomal abnormalities. In the chromosomally normal twin pregnancies, the prevalence of increased nuchal translucency was higher in fetuses of monochorionic than dichorionic pregnancies. The minimum estimated risk for trisomy 21, based on maternal age and fetal nuchal translucency thickness, was 1 in 300 in 19.5% of the twins, including all eight of those with trisomy 21⁷⁴.

Table 2 Prevalence of fetal nuchal translucency thickness (NT) above the 95th centile (for crown–rump length in singletons), in singleton, monochorionic twin pregnancies and dichorionic twin pregnancies.⁷⁴

	Fetuses with increased NT	Pregnancies with increased NT in at least one of the fetuses	Pregnancies with increased NT in both fetuses
Singleton	1122 (5.2%)	—	—
Twin ($n = 448$)	65 (7.3%)	52 (11.6%)	13 (2.9%)
Monochorionic ($n = 95$)	16 (8.4%)	13 (13.7%)	3 (3.2%)
Dichorionic ($n = 353$)	49 (6.9%)	39 (11.1%)	10 (2.8%)

These findings suggest that, in dichorionic twin pregnancies, the sensitivity and false-positive rate of fetal nuchal translucency thickness in screening for trisomy 21 are similar to those in singleton pregnancies. Therefore, effective screening and diagnosis of major chromosomal abnormalities can be achieved in the first trimester, allowing the possibility of earlier and therefore safer selective fetocide for those parents that choose this option.

In monochorionic pregnancies (unlike dichorionic twins), the false-positive rate of nuchal translucency screening is higher than in singletons. In monochorionic pregnancies, increased nuchal translucency in one of the fetuses should not lead to the erroneous conclusion of discordant risk for a chromosomal abnormality, but rather should stimulate the search for alternative causes, such as twin-to-twin transfusion syndrome.

In an extended series of 303 monochorionic pregnancies examined at the Harris Birthright Research Centre at King's College Hospital, the nuchal translucency was above the 95th centile in 52 (8.6%) of the 606 fetuses, and in at least one fetus in 41 (13.5%) of the 303 pregnancies. There were two cases of both fetuses being affected by trisomy 21; in one case, the nuchal translucency was increased in both fetuses (3.1 mm and 2.4 mm at 11 weeks), but in the second case the translucency was increased only in one of the fetuses (8.2 mm and 1.8 mm at 13 weeks). The number of cases examined is still too small to draw definite conclusions as to whether, in the calculation of risk of trisomy 21 in monochorionic pregnancies, the nuchal translucency of the fetus with the largest or the smallest measurement (or the average of the two) should be considered.

Fetal karyotyping in twins

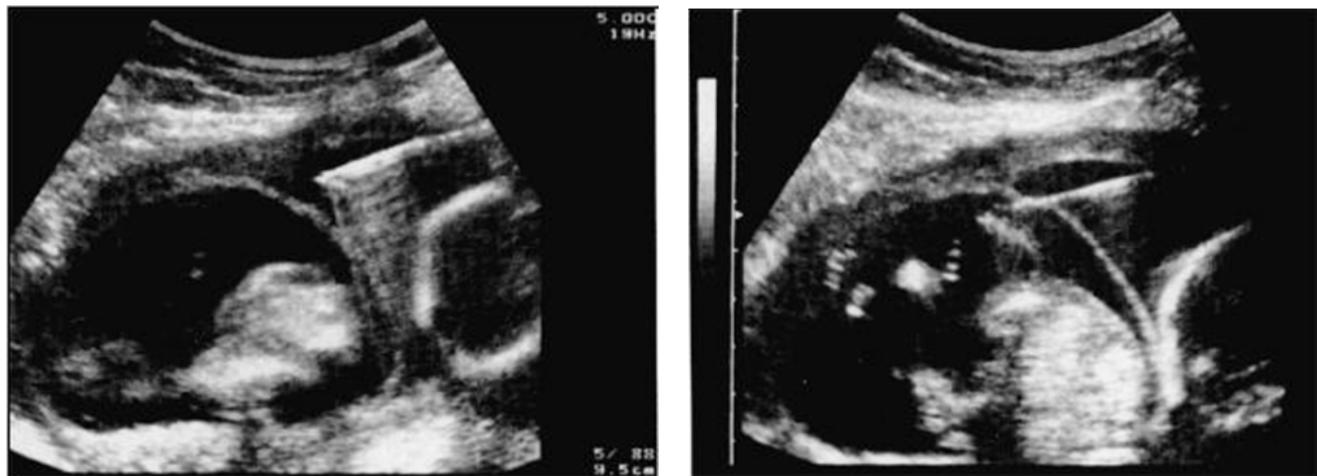
Fetal karyotyping requires invasive testing by amniocentesis or chorionic villus sampling. In singleton pregnancies, both techniques are highly successful in providing samples for cytogenetic analysis and the risk of fetal loss from the two procedures is similar (about 1% above the background risk). Therefore, in singleton pregnancies, the method of choice for fetal karyotyping may be chorionic villus sampling because of the advantages of early diagnosis, namely earlier reassurance for the majority of parents that the fetal karyotype is normal and the option of earlier termination for the few with an affected pregnancy.

In twin pregnancies, selection of the appropriate invasive technique depends on the:

1. Accuracy of obtaining a result from both fetuses;
2. Procedure-related risk of fetal loss; and
3. The risks of selective fetocide should the pregnancy be found to be discordant for an abnormality and the parents choose this option.

Amniocentesis in twins can be carried out through a single uterine entry ([Figure 12](#)). It is effective in providing a reliable karyotype for both fetuses and the procedure may be as safe as in singleton pregnancies⁷⁵. However, cytogenetic results are not available until around 18 weeks and the risk of miscarriage after selective fetocide at this gestation is three times higher than with fetocide before 16 weeks⁶⁶.

Figure 12 - Amniocentesis in twins using the single-needle technique. A 20-gauge needle with a stylet is guided into one amniotic sac (left). After aspiration of 10 ml of amniotic fluid, the syringe is removed, the stylet is replaced, and the needle is advanced through the inter-twin membrane under continuous ultrasound guidance into the second sac (right). The stylet is then removed and amniotic fluid aspirated; the first 1 ml is discarded to avoid possible contamination with fluid from the first sac



Chorionic villus sampling can be carried out in multiple pregnancies but, in about 5% of cases, there is uncertainty if both placentas have been sampled, especially in cases where the placentas are on the same side of the uterus⁷⁶⁻⁷⁹. To ensure that both fetuses are karyotyped, the extreme ends of the placentas should be reached through a single uterine entry of one needle, or two separate needle insertions are necessary; therefore the procedure-related risk of miscarriage may be higher than with amniocentesis. The advantage of chorionic villus sampling is that it provides results sufficiently early to allow for safer selective fetocide.

The choice of invasive technique in twins should therefore be based on the use of individual risk calculated by maternal age and fetal nuchal translucency thickness⁸⁰. When the risk for chromosomal defect in at least one of the fetuses is high (more than 1 in 50), it may be preferable to perform chorionic villus sampling. For pregnancies with a lower risk, amniocentesis at 16 weeks would be the favorite option.

There is an additional advantage of screening by measurement of nuchal translucency thickness in this context; when there is discordancy for a chromosomal abnormality, the presence of a sonographically detectable marker (increased nuchal translucency) helps to ensure the correct identification of the abnormal twin should the parents choose selective termination.

Management of twin pregnancies discordant for chromosomal abnormalities

In a study of 27 twin pregnancies affected by fetal trisomies, there were seven cases where both fetuses were trisomic and in these the parents opted for termination of pregnancy; termination was also performed in another pregnancy where one fetus had trisomy 18 and the chromosomally normal co-twin had a major facial cleft⁸¹. In 19 cases, one fetus had either trisomy 21 ($n = 14$) or trisomy 18 ($n = 5$) and the other was normal. Selective fetocide was carried out in 13 of the 14 pregnancies discordant for trisomy 21 and in one of the five with trisomy 18. In the four cases discordant for trisomy 18 that were managed expectantly, the trisomic baby died *in utero* or in the neonatal period, whereas the normal co-twin was liveborn at 33–40 (median 37) weeks. In the 14 cases of selective fetocide, the chromosomally normal co-twin was live born at 24–41 (median 38) weeks of gestation and there was an inverse relationship between the gestation at fetocide and gestation at delivery⁸¹.

The main issues in the management of twin pregnancies with fetal trisomies are:

1. When both fetuses are chromosomally abnormal, the parents usually choose termination of pregnancy.
2. In pregnancies discordant for chromosomal abnormalities, the main options are either selective fetocide or expectant management. In such cases, the decision is essentially based on the relative risk of selective fetocide causing miscarriage and hence death of the normal baby, compared to the potential burden of caring for a handicapped child.
3. Selective fetocide can result in spontaneous abortion or severe preterm delivery, which may occur several months after the procedure. The risk for these complications is related to the gestation at fetocide; selective fetocide after 16 weeks of gestation is associated with a three-fold increase in risk compared to reduction before 16 weeks, and there is an inverse correlation between the gestation at fetocide with the gestation at delivery⁶⁶. In embryo reduction of multifetal pregnancies, there is an increase in maternal serum α -fetoprotein which is proportional to the number of dead fetuses and this increase persists for 8–12 weeks, when there is complete resorption of the dead fetoplacental tissue⁸². It is possible that the resorbing dead fetoplacental tissue triggers an intrauterine inflammatory process, which is proportional to the amount of dead tissue and therefore the gestation at fetocide. Such an inflammatory process could result in the release of cytokines and prostaglandins which would, in turn, induce uterine activity with consequent miscarriage/ preterm labor.

In pregnancies discordant for trisomy 21, the usual choice is selective fetocide, because with expectant management the majority of affected babies would survive. In the case of trisomy 18, about 85% of affected fetuses die *in utero* and those that are liveborn usually die within the first year of life. In this respect, expectant management may be the preferred option; this would certainly avoid the procedure-related complications from selective fetocide. The alternative view is that the amount of dead fetoplacental tissue (and therefore the risk for consequent miscarriage or preterm labor) would be less after fetocide at 12 weeks rather than after spontaneous death of the trisomy 18 fetus at a later stage of pregnancy.

PRENATAL DETERMINATION OF CHORIONICITY

In twin pregnancies, prenatal diagnosis of chorionicity is important because:

1. Chorionicity, rather than zygosity, is the main factor determining pregnancy outcome. In monochorionic twins, the rates of miscarriage and perinatal death are much higher than in dichorionic twins. This increase in risk has been attributed to complications arising from the shared placental circulation, which is confined to monochorionic twins.
2. Death of a monochorionic fetus is associated with a high chance of sudden death or severe neurological impairment in the co-twin, which is important both for parental counselling should this occur spontaneously and for the management of discordant fetal abnormality.
3. Diagnostic testing of patients at high risk for genetic disorders and chromosomal abnormalities is dependent on chorionicity. In monochorionic twin pregnancies, when undertaking invasive diagnostic tests such as amniocentesis or chorionic villus sampling, it may be unnecessary to sample both fetuses since they are monozygotic and, therefore, have identical genetic compositions.
4. In the management of a twin pregnancy discordant for a major fetal defect, one of the options is selective fetocide, but in monochorionic twins this procedure should be avoided, otherwise both fetuses could die or the survivor could suffer severe neurological impairment.
5. In patients who did not have accurate determination of chorionicity in the first trimester but are subsequently found to have the 'lambda' sign present, the pregnancy can be considered to be in a lower-risk category for subsequent miscarriage or perinatal death. Furthermore, if the parents request invasive prenatal diagnosis of genetic syndromes and chromosomal defects, both twins should be sampled because such pregnancies are usually dizygotic. Since these pregnancies are dichorionic, one of the options to be considered in cases with discordant fetal malformations can be selective fetocide. In contrast, absence of the 'lambda' sign at 16–20 weeks does not exclude dizygosity. Therefore, invasive prenatal diagnosis should still involve sampling of both fetuses. However, in terms of management for discordant fetal malformation, these pregnancies must be considered monochorionic, and hence selective fetocide is precluded because, due to the shared placental circulation if the pregnancy is truly monochorionic, fetocide may result in death or neurological impairment of the healthy twin. In the absence of the lambda sign, selective fetocide can only be considered as an option if the placentas are separate or the twins are proven to be dizygotic, by the sonographic demonstration of discordant fetal sexes or by the presence of different genetic markers through examination of amniotic fluid or fetal blood.

MULTIFETAL PREGNANCY AND EMBRYO REDUCTION

An adverse consequence of the widespread introduction of assisted reproductive techniques has been an exponential increase in the prevalence of multifetal pregnancies¹³. Such pregnancies are associated with increased risk of miscarriage and perinatal death⁸³. In addition, there is increased risk of handicap. A study of births in Western Australia from 1980 to 1989 reported that the prevalence of cerebral palsy (per 1000 survivors up to 1 year of age) was 1.6 for singletons, 7.3 for twins and 28 for triplets⁸⁴. Similarly, a study of 705 twin pairs (1410 twins), 96 sets of triplets (287 triplets excluding one infant death) and seven sets of quadruplets (27 quadruplets excluding one infant death) reported that the prevalence of cerebral palsy (per 1000 survivors) was 9 in twins, 31 in triplets and 111 in quadruplets⁸⁵. The risk of cerebral palsy was mainly related to preterm delivery and therefore the chance for the parents that their pregnancy would result in at least one child with cerebral palsy was 1.5%, 8.0% and 42.9% in twin, triplet, and quadruplet pregnancies, respectively.

One of the options in the management of multifetal pregnancies is embryo reduction to twins, which is associated with a reduction in the background risk of adverse pregnancy outcome.

Technique and timing of embryo reduction

Iatrogenic fetal death is achieved by the ultrasound-guided injection of potassium chloride in the fetal heart or thorax. During the 3–4 months following reduction, there is gradual resorption of the dead fetuses and their placentas. It is technically feasible to perform reduction from as early as 7 weeks and the earlier the gestation the smaller the dead fetoplacental tissue mass, with the theoretical advantage of a lower rate of miscarriage. However, it is preferable that the procedure is delayed until 11–13 weeks to allow for spontaneous reduction. Furthermore, at this gestation, it is possible to diagnose major fetal abnormalities and also, through measurement of nuchal translucency thickness, to screen for chromosomal defects. If all fetuses appear to be normal, the ones chosen for reduction are those furthest away from the cervix to avoid the potential risk of amniorrhesis and ascending infection from the lower genital track. Ultrasound examination is also essential for the determination of chorionicity. In dichorionic triplets, selective fetocide of one of the monochorionic pair may lead to death or neurological sequelae in the co-twin, whereas iatrogenic death of the fetus with a separate placenta will result in a monochorionic twin pregnancy that is associated with a much higher risk of miscarriage or severe preterm delivery than dichorionic twins. Consequently, the parents may choose to convert the pregnancy into a singleton one by fetocide of both monochorionic twins.

Results of multifetal pregnancy reduction

The largest series combining data from nine centers throughout the world includes 1789 pregnancies undergoing fetal reduction from a mean starting number of four (two to more than six fetuses) to a finishing number of two (range 1–3) fetuses⁸⁶. In 11.7% of cases, there was miscarriage before 24 weeks, in 13.3% severe preterm delivery at 24–32 weeks, and in 75.0% delivery was beyond 32 weeks. The miscarriage rate and severe preterm delivery rate were related to both the starting and finishing number of fetuses.

Gestation at delivery, birth weight and pregnancy outcome of surviving fetuses from 127 multifetal pregnancies (3–8, median 4 fetuses) undergoing embryo reduction to twins were compared to 354 chromosomally normal non-reduced dichorionic twin pregnancies⁸⁷. In multifetal pregnancies reduced to twins, compared to the non-reduced twins, there was a five-fold increase in risk of miscarriage before 24 weeks (12.6% compared to 2.5%), a doubling of risk of severe preterm delivery before 33 weeks (17.1% compared to 7.6%) and a small reduction in birth weight for gestation (deficit of 0.94 SDs compared to 0.65 SDs). Furthermore, the interval between embryo reduction and miscarriage or delivery was associated with the gestation at reduction, which presumably reflects the amount of dead fetoplacental tissue.

Miscarriage within 2 weeks of embryo reduction is about 2%, which is similar to that of early amniocentesis in singleton pregnancies^{87,88}. Therefore, most miscarriages associated with multifetal pregnancy reduction are not due to the needling involved in reduction.

The most likely cause of pregnancy loss and severe preterm delivery in multifetal pregnancies following reduction is the development of an inflammatory response to the resorbing dead fetoplacental tissue, with subsequent release of cytokines and stimulation of prostaglandins. High levels of a-fetoprotein are found in the amniotic fluid of twin pregnancies after the spontaneous death of one of the fetuses and in multifetal pregnancies after reduction^{89–91}. Similarly, both spontaneous fetal death and disruption in the fetoplacental barrier are associated with high maternal serum a-fetoprotein levels^{92,93}. It has been previously reported that, in multifetal pregnancies, following the iatrogenic death of fetuses there is an increase in maternal serum a-fetoprotein concentration that is proportional to the amount of dead fetoplacental tissue and this increase persists for several months following the procedure⁸².

The main difference between the reduced and non-reduced pregnancies was miscarriage or severe preterm delivery up to 33 weeks. This finding is compatible with the hypothesis of a trigger of labor arising from the resorption of necrotic tissue, since the risk of early delivery was related to the gestation at reduction, and therefore the size of the dead fetoplacental units. An alternative mechanism of preterm delivery is the decline of hormonal support to the pregnancy following pregnancy reduction. Multifetal pregnancy reduction to twins is associated with a relative decrease in maternal serum concentrations of placental hormones, such as human chorionic gonadotropin, progesterone and estriol, which occurs within 2 weeks of the reduction and persists for at least 3 months⁹⁴.

Another possible explanation for fetal loss after reduction, as well as the finding that in multifetal pregnancies reduced to twins the birth weight for gestation is smaller than in non-reduced twins, is that, in the human, the maximum capacity of the endometrium/decidua to maintain a pregnancy is achieved with twins. In multifetal pregnancies, there is crowding and each fetal-placental-endometrial unit has less potential for growth and development than in twin pregnancies. After embryo reduction, the surviving twins have smaller placental units and therefore remain at a disadvantage compared to natural twins and this is manifested as spontaneous abortion, severe preterm delivery or growth restriction. Supportive evidence for this hypothesis is provided by changes in the maternal blood levels of placental protein 14 (PP14) and insulin-like growth factor binding protein-1 (IGFBP-1), which are the major protein products of the decidua of early pregnancy. Maternal plasma IGFBP-1 and PP14 concentrations in twin pregnancies are higher than those in singletons but the levels are not further increased with larger numbers of fetuses. In multifetal pregnancies reduced to twins, maternal serum concentrations of IGFBP-1 and PP14 decrease to levels characteristic of singleton rather than non-reduced twin pregnancies⁹⁵.

Reduction from trichorionic triplets to twins

In higher-order multifetal pregnancies, there is evidence that embryo reduction to twins is associated with a decrease in the background risk of perinatal death and handicap. However, in the case of triplet pregnancies reduced to twins, compared to those managed expectantly, the chance of survival is not improved but the risk of handicap may be lower.

Data from studies reporting on gestation at recruitment, and rates of miscarriage and severe preterm delivery in reduced and non-reduced triplet pregnancies ([Table 3](#))⁹⁶⁻¹¹³ suggest that fetal reduction to twins is associated with a significantly higher rate of miscarriage (8.3% versus 3.5%), but a 3-fold reduction in severe preterm delivery rate (20.5% versus 6.9%).

Table 3 - Studies reporting on outcome of triplet pregnancies managed with and without embryo reduction to twins. The studies included are those which provide data on gestation at recruitment and allow calculation of the rates of miscarriage and severe preterm delivery

Author	n	Gestation at recruitment/ reduction (weeks)	Miscarriage at < 24 weeks	Delivery at < 32 weeks
<i>Without embryo reduction</i>				
Lipitz <i>et al.</i> 1989 ⁹⁶	78	20*	—	20/78
Kingsland <i>et al.</i> 1990 ⁹⁷	43	16*	—	5/43
Seoud <i>et al.</i> 1991 ⁹⁸	26	6–8†	2/26	—
Melgar <i>et al.</i> 1991 ⁹⁹	20	9–14†	0/20	—
Porreco <i>et al.</i> 1991 ¹⁰⁰	11	10–11	0/11	1/11
Bollen <i>et al.</i> 1993 ¹⁰¹	39	7	2/39	9/37
Macones <i>et al.</i> 1993 ¹⁰²	14	16	0/14	6/14
Check <i>et al.</i> 1993 ¹⁰³	23	9–13	0/23	2/23
Boulot <i>et al.</i> 1993 ¹⁰⁴	48	8–13	3/48	7/45
Sebire <i>et al.</i> 1997 ¹⁰⁵	47	8–13	1/47	11/46
Total		10 (6–14)	8/228 (3.5%)	61/297 (20.5%)
<i>With embryo reduction</i>				
Porreco <i>et al.</i> 1991 ¹⁰⁰	13	10–11	1/13	1/12
Melgar <i>et al.</i> 1991 ⁹⁹	5	9–14†	0/5	—
Vauthier-Brouzes <i>et al.</i> 1992 ¹⁰⁶	14	10–12	0/14	2/14
Boulot <i>et al.</i> 1993 ¹⁰⁴	32	8–13	4/32	2/28
Check <i>et al.</i> 1993 ¹⁰³	6	9–13	0/6	0/6
Macones <i>et al.</i> 1993 ¹⁰²	47	9–12	4/47	3/43
Bollen <i>et al.</i> 1993 ¹⁰¹	33	7	3/33	1/30
Timor-Tritsch <i>et al.</i> 1993 ¹⁰⁷	43	9–10†	6/43	—
Lynch <i>et al.</i> 1990 ¹⁰⁸	88	10–13	7/88	4/81
Berkowitz <i>et al.</i> 1993 ¹⁰⁹				
Tabsh 1990, 1993 ^{110,111}	66	11–13†	4/66	—
Shalev <i>et al.</i> 1989 ¹¹²	34	10–13	3/34	3/31
Lipitz <i>et al.</i> 1994 ¹¹³				
Sebire <i>et al.</i> 1997 ¹⁰⁵	66	7–13	5/66	5/61
Total		10 (7–14)	37/447 (8.3%)	21/306 (6.9%)

*Data from these studies were used only for the calculation of gestation at delivery not miscarriage rates; †data from these studies were used only for the calculation of miscarriage rates not gestation at delivery

On the basis of these results and also the gestational age distribution of reduced and non-reduced triplet pregnancies delivering at 24–31 weeks^{102,105,113}, and the survival and handicap rates of singleton pregnancies of the same gestational age¹¹⁴, it was estimated that:

1. In trichorionic triplets managed expectantly, the survival probability is 92.4% with a 95.8% chance that at least one baby will be born alive and a 2.1% chance that at least one will be handicapped¹⁰⁵.
2. In triplets reduced to twins, the survival probability is 89.7% with a 91.4% chance that at least one baby will be born alive and a 0.5% chance that at least one will be handicapped¹⁰⁵.

On the basis of currently available data, parents can be counselled that, in trichorionic triplet pregnancies, with all three fetuses being alive at 12 weeks of gestation, the rates of miscarriage and delivery before 32 weeks are about 4% and 20%, respectively. Furthermore, in triplets reduced to twins, there is an increase in miscarriage rate to about 8% but a decrease in the rate of severe preterm delivery to 10%¹⁰⁵. Irrespective of the chosen management, there is a more than 90% chance of live births and the potential risk of severe handicap in the survivors is about 1–3%.

Chapter 5 References

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The 11-14-week scan

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1. Accuracy of obtaining a result from both fetuses;
2. Procedure-related risk of fetal loss; and
3. The risks of selective fetocide should the pregnancy be found to be discordant for an abnormality and the parents choose this option.

Amniocentesis in twins can be carried out through a single uterine entry ([Figure 12](#)). It is effective in providing a reliable karyotype for both fetuses and the procedure may be as safe as in singleton pregnancies⁷⁵. However, cytogenetic results are not available until around 18 weeks and the risk of miscarriage after selective fetocide at this gestation is three times higher than with fetocide before 16 weeks⁶⁶.

Compared to singletons, prenatal diagnosis of chromosomal abnormalities is complicated because, first, effective methods of screening, such as maternal serum biochemistry, are not applicable; second, the techniques of invasive testing may provide uncertain results or may be associated with higher risks of miscarriage; and, third, the fetuses may be discordant for an abnormality, in which case one of the options for the subsequent management of the pregnancy is selective fetocide.

Screening for chromosomal defects

In dizygotic pregnancies, the maternal age-related risk for chromosomal abnormalities for each twin may be the same as in singleton pregnancies and, therefore, the chance that at least one fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. Furthermore, since the rate of dizygotic twinning increases with maternal age, the proportion of twin pregnancies with chromosomal defects is higher than in singleton pregnancies.

In monozygotic twins, the risk for chromosomal abnormalities is the same as in singleton pregnancies and, in the vast majority of cases, both fetuses are affected. There are, however, occasional case reports of monozygotic twins discordant for abnormalities of autosomes or sex chromosomes, most commonly with one fetus having Turner syndrome and the other either a normal male or female phenotype, but usually with a mosaic karyotype⁶⁸⁻⁷¹.

The relative proportion of spontaneous dizygotic to monozygotic twins in the United Kingdom is about 2:1 and, therefore, the prevalence of chromosomal abnormalities affecting at least one fetus in twin pregnancies would be expected to be about 1.6 times that in singletons.

Since it is now possible to determine chorionicity antenatally by ultrasonography, in counselling parents, it is possible to give more specific estimates of one and/or both fetuses being affected, depending on chorionicity. Thus, in monochorionic twins, the parents can be counselled that both fetuses would be affected and this risk is similar to that in singleton pregnancies. If the pregnancy is dichorionic, then the parents can be counselled that the risk of discordancy for a chromosomal abnormality is about twice that in singleton pregnancies, whereas the risk that both fetuses would be affected can be derived by squaring the singleton risk ratio. For example, in a 40-year-old woman with a risk for trisomy 21 of about 1 in 100 based on maternal age, in a dizygotic twin pregnancy the risk that one fetus would be affected would be 1 in 50 (1 in 100 plus 1 in 100), whereas the risk that both fetuses would be affected is 1 in 10,000 (1 in 100 x 1 in 100). This is, in reality, an oversimplification, since, unlike monochorionic pregnancies that are always monozygotic, only about 90% of dichorionic pregnancies are dizygotic.

Screening by second-trimester biochemistry

In singleton pregnancies, screening for trisomy 21 by a combination of maternal age and second-trimester maternal serum biochemistry can detect about 60% of trisomy 21 cases for a 5% false-positive rate.

In twin pregnancies, the median values for maternal serum markers, such as a-fetoprotein, hCG, free b-hCG and inhibin-A, are about twice those for singleton pregnancies⁷². When this is taken into account in the mathematical modelling for calculation of risks, it is estimated that serum screening in twins may identify about 45% of affected fetuses for a 5% false-positive rate⁷².

Even if prospective studies demonstrate that serum testing in twins is effective, the following problems would still need to be addressed:

1. The detection rate for an acceptable low false-positive rate, especially since invasive testing in multiple pregnancies is technically more demanding;
2. In the presence of a 'screen-positive' result, there is no feature to suggest which fetus may be affected; and
3. If the pregnancy is discordant for a chromosomal defect, further management by way of selective termination carries increased risk in the second compared to the first trimester.

Screening by first-trimester biochemistry

In a prospective screening study by measurement of fetal nuchal translucency thickness, maternal serum free b-hCG was measured in 4181 singleton and 148 twin pregnancies; in the latter group, there were 12 pregnancies with trisomy 21 in either one ($n = 10$) or both ($n = 2$) fetuses⁷³. In the normal twin pregnancies, compared to singletons, the median maternal serum free b-hCG adjusted for maternal weight was 1.94 MoM. In the 12 trisomy 21 twin pregnancies, the median level of free b-hCG was significantly higher than in normal twins but the level was above the 95th centile in only one case. These results suggest that measurement of maternal serum free b-hCG is unlikely to be useful in the prediction of fetal trisomy 21 at 11–14 weeks.

Screening by fetal nuchal translucency thickness

In a screening study for trisomy 21 involving 448 twin pregnancies, nuchal translucency thickness was measured in each fetus and the risk was estimated by combining with maternal age. The nuchal translucency was above the 95th centile of the normal range (for crown-rump length in singletons) in 7.3% fetuses, including 88% of those with trisomy 21 ([Table 2](#))⁷⁴. Increased translucency was also present in four fetuses with other chromosomal abnormalities. In the chromosomally normal twin pregnancies, the prevalence of increased nuchal translucency was higher in fetuses of monochorionic than dichorionic pregnancies. The minimum estimated risk for trisomy 21, based on maternal age and fetal nuchal translucency thickness, was 1 in 300 in 19.5% of the twins, including all eight of those with trisomy 21⁷⁴.

Table 2 Prevalence of fetal nuchal translucency thickness (NT) above the 95th centile (for crown-rump length in singletons), in singleton, monochorionic twin pregnancies and dichorionic twin pregnancies.⁷⁴

	<i>Fetuses with increased NT</i>	<i>Pregnancies with increased NT in at least one of the fetuses</i>	<i>Pregnancies with increased NT in both fetuses</i>
Singleton	1122 (5.2%)	—	—
Twin (<i>n</i> = 448)	65 (7.3%)	52 (11.6%)	13 (2.9%)
Monochorionic (<i>n</i> = 95)	16 (8.4%)	13 (13.7%)	3 (3.2%)
Dichorionic (<i>n</i> = 353)	49 (6.9%)	39 (11.1%)	10 (2.8%)

These findings suggest that, in dichorionic twin pregnancies, the sensitivity and false-positive rate of fetal nuchal translucency thickness in screening for trisomy 21 are similar to those in singleton pregnancies. Therefore, effective screening and diagnosis of major chromosomal abnormalities can be achieved in the first trimester, allowing the possibility of earlier and therefore safer selective fetocide for those parents that choose this option.

In monochorionic pregnancies (unlike dichorionic twins), the false-positive rate of nuchal translucency screening is higher than in singletons. In monochorionic pregnancies, increased nuchal translucency in one of the fetuses should not lead to the erroneous conclusion of discordant risk for a chromosomal abnormality, but rather should stimulate the search for alternative causes, such as twin-to-twin transfusion syndrome.

In an extended series of 303 monochorionic pregnancies examined at the Harris Birthright Research Centre at King's College Hospital, the nuchal translucency was above the 95th centile in 52 (8.6%) of the 606 fetuses, and in at least one fetus in 41 (13.5%) of the 303 pregnancies. There were two cases of both fetuses being affected by trisomy 21; in one case, the nuchal translucency was increased in both fetuses (3.1 mm and 2.4 mm at 11 weeks), but in the second case the translucency was increased only in one of the fetuses (8.2 mm and 1.8 mm at 13 weeks). The number of cases examined is still too small to draw definite conclusions as to whether, in the calculation of risk of trisomy 21 in monochorionic pregnancies, the nuchal translucency of the fetus with the largest or the smallest measurement (or the average of the two) should be considered.

Fetal karyotyping in twins

Fetal karyotyping requires invasive testing by amniocentesis or chorionic villus sampling. In singleton pregnancies, both techniques are highly successful in providing samples for cytogenetic analysis and the risk of fetal loss from the two procedures is similar (about 1% above the background risk). Therefore, in singleton pregnancies, the method of choice for fetal karyotyping may be chorionic villus sampling because of the advantages of early diagnosis, namely earlier reassurance for the majority of parents that the fetal karyotype is normal and the option of earlier termination for the few with an affected pregnancy.

In twin pregnancies, selection of the appropriate invasive technique depends on the:

1. Accuracy of obtaining a result from both fetuses;
2. Procedure-related risk of fetal loss; and
3. The risks of selective fetocide should the pregnancy be found to be discordant for an abnormality and the parents choose this option.

Amniocentesis in twins can be carried out through a single uterine entry ([Figure 12](#)). It is effective in providing a reliable karyotype for both fetuses and the procedure may be as safe as in singleton pregnancies⁷⁵. However, cytogenetic results are not available until around 18 weeks and the risk of miscarriage after selective fetocide at this gestation is three times higher than with fetocide before 16 weeks⁶⁶.

1. The prevalences of monochorionicity and dichorionicity in twin pregnancies discordant for anencephaly are similar, and, by implication, the prevalence of anencephaly is much higher in monochorionic than dichorionic pregnancies. In a study of 2874 twin and 334 912 singleton pregnancies from the same population over the same period, the prevalence of anencephaly was 10.4/10 000 in twins compared to 2.8/10 000 in singletons⁶³. This increase was mainly found in like-sex compared to unlike-sex pairs and, by implication, in monozygotic compared to dizygotic pregnancies. Furthermore, the prevalence of concordancy for anencephaly in monozygotic twins is twice as high as in dizygotic pregnancies⁶⁴, and, consequently, there may be a genetic contribution to the pathogenesis of neural tube defects; however, concordancy for anencephaly is found in less than 10% of affected pregnancies and, therefore, the contribution of environmental factors may be of greater importance than that of genetic factors.
2. Anencephaly is associated with a high risk of preterm delivery before 32 weeks, which is usually due to the development of polyhydramnios secondary to reduced fetal swallowing. In a study of 60 singleton pregnancies with anencephaly, before the advent of prenatal diagnosis, the prevalence of clinical polyhydramnios was 49%⁶⁵.
3. In dichorionic twins discordant for anencephaly, the two management options are selective fetocide or serial ultrasound examinations for early diagnosis of polyhydramnios, which can then be treated either by amniodrainage or selective fetocide. Selective fetocide is associated with mortality of the normal twin through procedure-related miscarriage. The risk of miscarriage after selective fetocide is about 5% or 15% depending on whether the procedure is carried out before or after 16 weeks of gestation, respectively⁶⁶. Since first-trimester ultrasound examination is increasingly being introduced as part of routine antenatal care and anencephaly can be reliably diagnosed at 11–14 weeks of gestation⁶⁷, it is possible that the majority of twin pregnancies discordant for anencephaly will now be diagnosed sufficiently early for safer selective fetocide. An additional advantage of earlier selective fetocide is that the risk of severe preterm delivery is reduced and, on average, the gestation at delivery of the normal twin is later than with fetocide after 16 weeks⁶⁶.
4. In monochorionic twin pregnancies, selective fetocide is not possible because death of the anencephalic fetus would be followed by death of the normal co-twin; this may be due to transplacental passage of the injected potassium chloride or acute exsanguination through the vascular anastomoses into the placenta of the dead anencephalic fetus. However, since expectant management is associated with spontaneous intrauterine death of the anencephalic fetus in about 25% of cases, this option can also result in the death of the normal twin through similar mechanisms. Future research may demonstrate that the optimal management of monochorionic twin pregnancies discordant for anencephaly is selective fetocide by occlusion of the umbilical cord vessels of the abnormal fetus.

In twin pregnancies discordant for lethal abnormalities, the aims are to maximize the chances of survival of the normal twin and prevent severe preterm delivery. Early diagnosis through routine ultrasound examination at 11–14 weeks will inevitably stimulate further research in this area. The questions to be resolved by multicenter randomized studies are whether the risk of death and severe preterm delivery are less with expectant management or selective fetocide in the first trimester. In the case of dichorionic pregnancies, fetocide can be carried out by the traditional method of intracardiac injection of potassium chloride, whereas, in monochorionic pregnancies, fetocide would necessitate occlusion of the umbilical cord vessels.