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Perinatal Mortality in Multiple Pregnancy

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1. Introduction

Twins and higher–order multiple pregnancies account for approximately 3% of all gestations in the United States (Ananth et al, 2004) and seem to be stabilized since 2006 after a dramatically increase since the beginning of the 1970s (Vayssière et al, 2011). There are two main causes for the change in the rate of multiple pregnancies: advanced maternal age and use of assisted reproductive techniques (ART) (Chauhan et al, 2010).

In occidental society, there is increasing tendency for women to delay pregnancy after 35 years. Use of fertility treatment is also more frequent in this advanced age group. The need to maximise treatment success has led to a culture of acceptance of multiple pregnancies, including high order multiples. In ART, the overall twin rate is around 26%. In the United States, the twin rate is 32%; in Latin America, it is 25%; in Europe, it is 23%; in Asia and the Middle East, it is 22%, and in Australia/New Zealand, it is 21% (Chauhan et al, 2010). Women should therefore be informed reasonably early in their childbearing years of the risks associated with late pregnancy. The perinatal mortality for multiple pregnancy exceeds that of singleton pregnancy and the optimal management should minimise losses.

2. Perinatal risks of multiple pregnancies

Health risks associated with multiple pregnancies involve both fetal and neonatal mortality. The main cause is prematurity and extreme prematurity (birth before 28 weeks gestation). The prognosis for these very preterm infants is poor, with a very low chance of intact survival if born before 26 weeks. The risk of cerebral palsy in twins has been estimated at four times that of singletons, and even moderate prematurity is associated with long term educational and behavioural problems and infant death (Black et al, 2010). Multiple pregnancies pose a number of unique challenges, such as discordant growth abnormalities, intrauterine demise, preterm premature rupture of the membranes, or premature delivery of one or both twins. At a more complex level, multiple pregnancies sharing a single placental circulation are associated with additional problems in their diagnosis and management, including twin-twin transfusion syndrome. All adverse outcomes of pregnancy, including mortality, are more likely in multiples compared with singleton pregnancies, and associated risks increase in higher order multiples.

3. Risk factors for perinatal mortality

Systematic ultrasound assessment is essential for diagnosis risk factors for fetal mortality (Hubinont et al, 2010).

3.1 Diagnosis of chorionicity and amnionicity

Chorionicity denotes the type of placentation. Monochorionic twins are always monozygotic, while dichorionic twins can be either monozygotic or dizygotic.

Diagnosis of amnionicity and chorionicity in multiple gestations is essential as monochorionic pregnancies have a greater risk for fetal morbidity and mortality than dichorionic pregnancies. The earliest and most accurate predictor for multiple gestations is the assessment of amnionicity and chorionicity. Accuracy in this diagnosis is essential, and will form the cornerstone of pregnancy counselling, decision-making, and management. Management and treatment options are now available in pregnancies with monochorionic placentation and can result in improved fetal outcome.

Every report of an ultrasound examination of a multiple pregnancy during the first trimester should include information about chorionicity and amnionicity. It is recommended that chorionicity be diagnosed as early as possible in multiple pregnancies, because the earlier the diagnosis, the more reliable it is.

During the first trimester, the most relevant signs are the number of gestational sacs between 7 and 10 weeks and the presence of a lambda sign between 11 and 14 weeks. The 'Lambda' or 'Twin peak' sign was first described by Bessis (1981) and referred to the triangular projection of tissue extending up to the base of the inter-twin membrane in dichorionic placentation. This sign is most useful in assessing pregnancies after 10 weeks. Visualization of a thin wispy membrane that comes to a T-shape 90° junction at the base indicates the presence of a diamniotic-monochorionic gestation.

In dichorionic twin pregnancy, the intertwin membrane includes two chorion layers interposed between amnion. Thus a thick intertwin membrane is more likely to be seen in dichorionic than a monochorionic-diamniotic twin pregnancy.

Sensitivity for determining chorionicity based on membrane thickness declines with increasing gestation. There is no clear cut-off for membrane thickness, although several studies reported a 2 mm cut-off, while others suggest a lower cut-off of 1.5 mm. The absence of any dividing membrane on repeated investigations, the absence of a T-sign, and the presence of a single yolk sac are associated with a monochorionic-monoamniotic gestation.

Two separate placentas or gender discordance ensures dichorionicity of the twin pregnancies, but the converse is not always true. Dichorionic twin pregnancies can be of the same gender and a single placenta could be the result of two contiguous fused placenta of a dichorionic twin pregnancy.

Membrane analysis in the second trimester is similar to that performed in the first trimester for thickness and the presence of either the twin-peak or T-shaped sign. Many authors have reported that chorionicity assessment is less accurate in second and third trimester. After 20 weeks of gestation the 'twin-peak sign' disappeared in about 7% of dichorionic pregnancies due to regression of the chorion frondosum (Sepulveda et al, 1997).

The number of layers in the dividing membrane can also be used to assess chorionicity; however it is not particularly helpful. The inter-fetal membrane needs to be magnified under high resolution and ideally perpendicular to the ultrasound probe to identify the number of layers.

If chorionicity is appropriately diagnosed during the first trimester of pregnancy and the 'explicit photograph of the ultrasound image allowing diagnosis of chorionicity' can be available, this diagnosis should not to be reconsidered later.

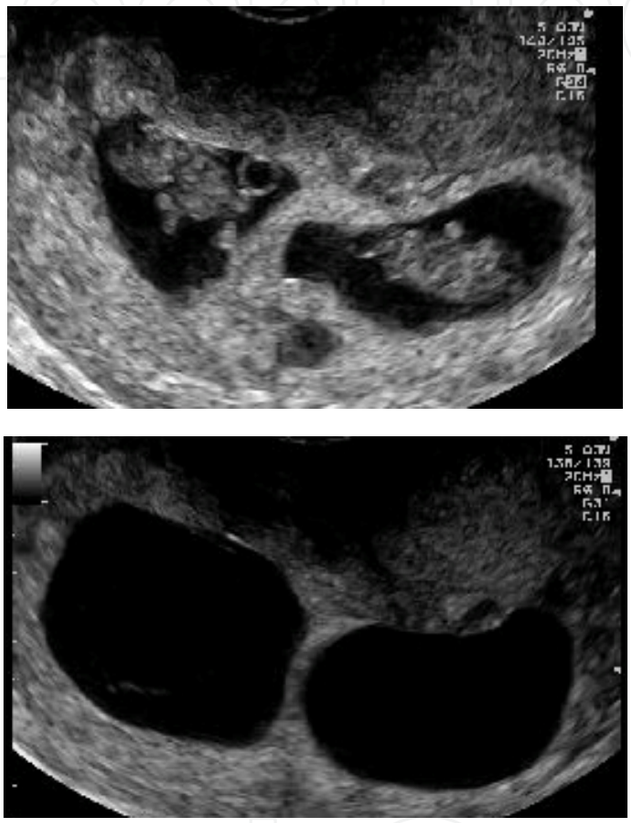

Fig. 1. Chorionicity determination in the first trimester. Ultrasound images of dichorionic pregnancies. The 'full' lambda sign reflects the apposition of the two placental disks.

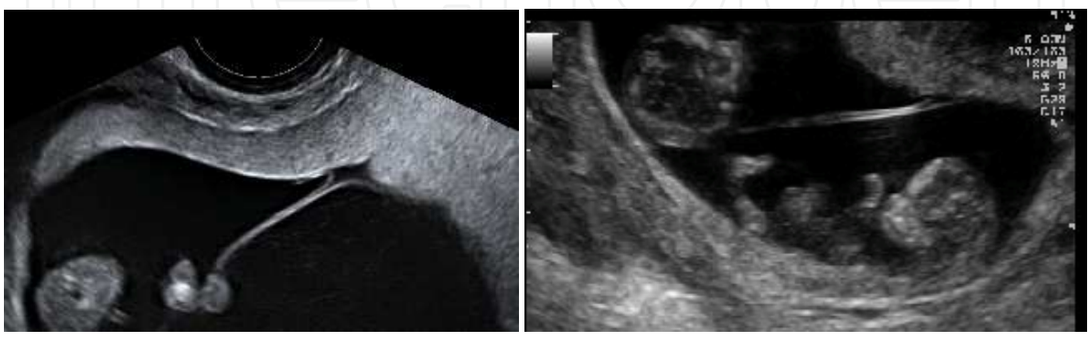

Fig. 2. Ultrasound images of a monochorionic diamniotic twin pregnancy. The 'empty' lambda sign or the T sign: only two thin layers of amniotic membranes separate the twins.

3.2 Congenital malformations

Twin pregnancies have an increased risk of congenital malformations, especially monochorionic twins (Sperling et al, 2007). Congenital anomalies may be the result of the teratogenic insult responsible for the twinning. For any given defect in a twin pregnancy, the pregnancy may be concordant or discordant, although the majority of structural defect are discordant, regardless of zygosity. Discordance in non-identical (dizygotic) twins is usually due to differences in genetic predisposition, whereas in identical (monozygotic twins) twins, it may be a consequence of the underlying stimulus to zygote splitting, variation in gene expression, or abnormal placentation (Hendrix et al, 1998).

Structural anomalies have been reported to occur more often in monozygotic twins with relative risks of congenital anomalies in twins compared with singletons of 1.17 for dizygotic twins (Myrianthopoulos et al, 1978) and 1.25 for monozygotic twins (Mastroiacovo et al, 1999). Major congenital defects are found in about 6% of twin pregnancies and usually, only one twin is affected (Lewi et al, 2007). Cardiac anomalies are significantly prevalent amongst monochorionic twins (Manning et al, 2006 and Bahtiyar et al, 2007). The incidence of congenital malformations was 3.2% among monozygotic and 2.2% among dizygotic twins. Cardiac abnormalities accounted for 68% of all abnormalities (Sperling et al, 2007).

3.3 Aneuploidy screening

3.3.1 Maternal serum markers

Serum screening is of limited value in twin pregnancies because the mean sensitivity is associated with a high false-positive rate and the screening test does not provide the separate risk for each fetus. Screening in twin pregnancies requires adjustment of the multiple of the median (MoM) to account for the presence of two fetuses. Different factors are required for the observed corrected MoM for free β human chorionic gonadotropin and pregnancy-associated plasma protein-A (Spencer et al, 2008). The routine use of serum markers during first trimester is not recommended but their use is currently being assessed (Vayssière et al, 2011)

3.3.2 Nuchal translucency (NT)

Enlarged nuchal translucency appears in fetuses affected by pathological conditions such as some chromosomal abnormalities, congenital heart defects, major extracardiac malformations and genetic syndromes. In singleton pregnancies, enlarged nuchal translucency (greater than the 95th centile) is encountered in about 5% of cases and in dichorionic pregnancies the frequency is about the same. In fetuses of monochorionic diamniotic pregnancies the frequency of an enlarged nuchal translucency is significantly higher, about 15%, without epidemiological demonstration of a higher frequency of chromosomal abnormalities (Sebire et al, 2000). In a monochorionic pregnancy, in which fetuses share the same placenta, enlarged nuchal translucency may affect one or both fetuses. First-trimester imbalance in the placental circulation between the two fetal compartments may be one of the causes of the nuchal translucency enlargement. Discordance in nuchal translucency is more frequent in cases that are later complicated by twin-to-twin transfusion syndrome or have an unfavourable outcome. The risk of developing severe TTTS requiring fetoscopic laser surgery can be predicted from the

intertwin discordance in fetal nuchal translucency at 11 to 13 + 6 weeks. The risk is more than 30% in those pregnancies with discordance in nuchal translucency of 20% or more, compared to less than 10% in those with a smaller discordance (Kagan et al, 2007). Nuchal translucency enlargement may also be attributable to the presence of fetal structural defects especially cardiac defects (Bahtiyar et al, 2007). When enlarged nuchal translucency is found in both fetuses, the presence of an abnormal karyotype may be the underlying pathological condition. Discordance in nuchal translucency and discrepant karyotype (heterokaryotypia) may result from a mitotic error arising after splitting and resulting in the chromosomal abnormality only in one of the fetuses. Although the frequency of heterokaryotypia is very low, this possibility should be kept in mind when a discordant nuchal translucency thickness is found (Cheng et al, 2006).

4. Complications and contribution of multiple pregnancies to the burden perinatal mortality

4.1 Preterm delivery

Twins are more likely to be delivered preterm (< 37 weeks of gestation) than singletons. In 2006, in the United States, approximately 60% of the twins were preterm and weighed less than 2500g. Approximately 1 out of 10 twin was born at below 32 weeks of gestation or weighed less than 1500g (Chauhan et al, 2010). The perinatal mortality in twins is related to comorbidity factors such as premature rupture of membranes, socioeconomical and ethnical factors, gestational age, fetal gender and availability of antenatal management with corticosteroids. In some complicated and high-risk twins pregnancies, elective preterm birth is indicated to avoid specific complications described later.

4.2 Complications of monochorionicity

Monochorionic twins account for 20% of spontaneous twin pregnancies and almost 5% occur as a result of assisted reproductive techniques (Cordero et al, 2005). The incidence of monochorionic twin pregnancies is increasing, as there are more pregnancies in older women associated with twins (Aston et al, 2008).

These fetuses are at higher risks of adverse outcome, compared with dichorionic twins and singleton pregnancies. The main reason for this is an unbalanced flow in the placental vascular anastomoses connecting both fetal circulations. Vascular complications in monochorionic twins are well known and may cause different disorders. The most important is twin-twin transfusion syndrome (TTTS), complicated around 10-15% of twins with monochorionic placentation. Other complications include growth retardation, twin anemia polycythemia sequence, twin reversed arterial perfusion, congenital heart disease due to vascular instability, fetal demise, and long-term neonatal and pediatric morbidity secondary to vascular insults in fetal brain, heart and kidneys (Lewi et al, 2010). Vascular disruptive sequences cumulating in TTTS can include infarction of the intestine or skin resulting in widespread skin aplasia or intestinal atresia, or infarction of the brain, kidneys, liver and lungs (Sperling et al, 2007).

A recent systematic review demonstrated that the incidence of congenital heart malformations is about 5%, some 9-fold higher than expected for a singleton pregnancy.

Given this last observation (Bahtiyar et al, 2007), detailed echocardiography would seem to be an appropriate routine investigation in all monochorionic pregnancies.

4.2.1 Twin-to-twin transfusion syndrome (TTTS)

TTTS, also called twin oligoamnios polyhydramnios sequence (TOPS), complicates around 15% of monochorionic pregnancies irrespective of the mode of conception. It is a hemodynamic, and probably hormonal, discordance secondary to imbalanced blood flow through the vascular anastomoses (Hubinont et Fisk, 1990) (Chalouhi et al, 2011). The natural history of untreated TTTS leads to intra- or perinatal death in 90% of cases (Robyr et al, 2006). Impaired neurological development is reported in up to 50% of survivors as a consequence of prematurity or the intrauterine fetal demise of one twin (Haverkamp et al, 2001).

TTTS can be diagnosed at any time in gestation. Membrane folding or intertwin disparity in fetal growth, nuchal translucency thickness or amniotic fluid volumes are early signs of the possible development of TTTS and indicate the need for increased ultrasound surveillance of monochorionic pregnancies. This syndrome can also be suspected by acute maternal symptoms related to polyhydramnios (uterine distension, uterine contractions, dyspnea) (Chalouhi et al, 2011).

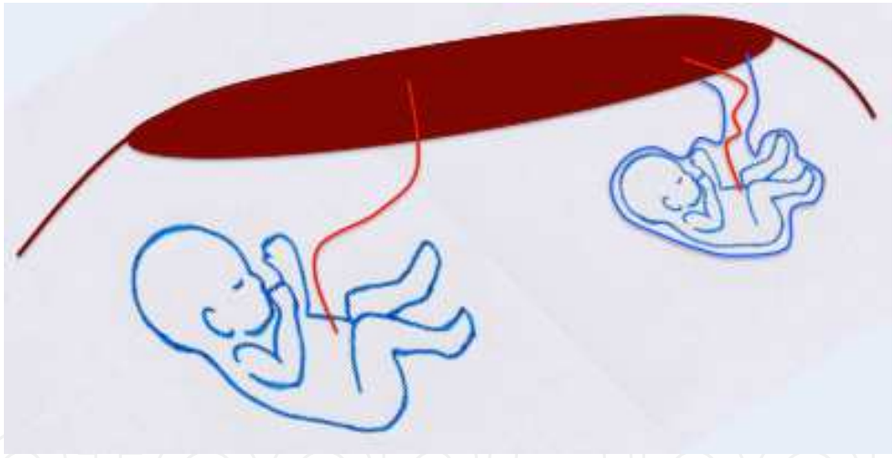

Fig. 3. 'Stuck twin' in a TTTS in a monochorionic diamniotic twin pregnancy.

The diagnosis relies upon strict ultrasound criteria as defined in the Eurofetus trial (Senat et al, 2004) and consist of a polyuric polyhydramnios in the recipient twin with a deepest vertical pool of at least 8.0 cm at or before 20 weeks of gestation or 10.0 cm after 20 weeks of gestation together with a distended fetal bladder, with oliguric oligohydramnios in the donor twin, showing a deepest vertical pool of at most 2.0 cm. Ultrasound staging of TTTS was introduced in 1999 by Quintero and provided a reproductible classification.

TTTS may also occurs in monoamniotic twins. In these patients, the absence of a dividing membrane does not allow development of oligohydramnios in the donor. Rather, the single amniotic cavity has polyhydramnios. The diagnosis is made by noting polyhydramnios and differences in bladder filling or Doppler studies.

Stage	Poly/oligo Hydramnios	Absent bladder in the donor	Abnormal Dopplers flow	Hydrops	Demise
I	+	-	-	-	-
II	+	+	-	-	-
III	+	+	+	-	-
IV	+	+	+	+	-
V	+	+	+	+	+

Table 1. Quintero staging of TTTS based on sonographic and Doppler findings (Quintero et al, 1999)

The prognosis is not accurately related to the Quintero's staging because the natural history of TTTS does not follow an orderly progression through the stages over time. A number of 'early stage' cases do not progress and remain at stage 1 or even regress. As Quintero's staging does not take into account the fundamental cardiovascular perturbations, recent articles have focused on the value of the recipient's cardiac function (Barrea et al, 2006). This has led to the development of independent scoring systems based upon echocardiographic and peripheral Doppler findings. Rychik et al (2007) proposed the Children's Hospital of Philadelphia scoring system, designed to represent the cardiovascular status of the twins and which correlated with the Quintero staging system. Shah et al (2008) designed a very similar scoring system with the cardiovascular profile score. Stirnemann et al (2010) developed cardiac profiling allowing discrimination of cases with significant myocardial dysfunction as well as assessment of the severity of the recipient's cardiomyopathy.

4.2.2 Twin anemia polycythemia sequence (TAPS)

Twin anemia-polycythemia sequence (TAPS) is an atypical form of twin-twin transfusion syndrome. There is a large intertwin hemoglobin difference with one twin developing chronic anemia with reticulocytosis and the other developing polycythemia, without oligohydramnios-polyhydramnios sequence (Lopriore et al, 2007). The prenatal diagnostic criteria for TAPS require that the middle cerebral artery-peak systolic velocity (MCA-PSV) measure greater than 1.5 multiples of median (MoM) in the donor twin and less than 0.08 MoM in the recipient twin (Robyr et al, 2006). A chronic rather than an acute intertwin transfusion is diagnosed by an elevated reticulocyte count in the anemic twin. The presumed etiology of TAPS involves the presence of small unidirectional artery-to-vein anastomoses, suggesting that TAPS results from a chronic net transfusion across these tiny anastomoses. TAPS can occur spontaneously in about 5% of previously uncomplicated monochorionic pregnancies. It is, however better known in its iatrogenic form as a complication of incomplete laser treatment for TTTS. TAPS begins usually after 30 weeks, especially in pairs with late-onset discordant growth (Lewi et al, 2007). Because of its late presentation, the mortality of TAPS is likely to be lower than that of TTTS (Lewi et al, 2010). Symptomatic treatment consists of intrauterine transfusion of the anemic twin combined eventually with hemodilution of the polycythemic co-twin. Laser therapy was used as causative treatment to interrupt the shared circulation. Selective feticide by cord occlusion can be offered in cases with severe associated anomalies (Gucciardo et al, 2010)

4.2.3 Selective intrauterine growth restriction

Selective intrauterine growth restriction (sIUGR) is a common condition associated with monochorionic pregnancy. It is increasingly considered to be an important complication of monochorionic twins, with potentially significant risks of intrauterine fetal demise or neurological adverse outcome for both twins (Lewi et al, 2008).

The term 'selective intrauterine growth restriction' in monochorionic pregnancies is applicable to cases where the estimated fetal weight (EFW) of the small fetus falls below the 10th percentile. Significant fetal weight discordance is an important element of the clinical picture, which will often accompany this condition, but is not necessary for diagnosis. Fetal weight discordance is defined as a difference between the EFW of two fetuses > 25% and is calculated as the difference between the EFW of the larger twin and the smaller twin divided by the EFW of the larger twin. The prevalence of sIUGR based on an EFW below the 10th percentile ranges from 10 to 15%. However, in contrast to TTTS, it has a much lower mortality, about 10 versus 55% (Lewi et al, 2007).

The most feared complication of sIUGR is the intrauterine demise of the growth-restricted twin. However substantial risks for the normally grown twin are well known even if both fetuses are born alive. These risks stem from two main factors. First, since these pregnancies must by definition be delivered before the death of the IUGR fetus, the normal twin is exposed to severe prematurity with its known consequences in terms of neurodevelopmental sequelae. Second, even if prematurity is avoided, there may be an increased prevalence of neurological complications in the normally grown twin due to a high risk of acute feto-fetal transfusion accidents in utero (Ishii et al, 2009). The specific risks for these two complications may vary in different types of sIUGR, as discussed later.

The principle cause for the development of sIUGR in monochorionic twins is inadequate placental sharing. Aside from placental territory discordance, a second factor largely influencing fetal weight discordance and the natural history of sIUGR in monochorionic twins is the presence of vascular anastomoses in the monochorionic placenta (Lewi et al, 2007). The presence of placental anastomoses has a protective effect on the IUGR fetus, which receives blood from its co-twin that may partially compensate the placental insufficiency.

As a consequence of the combination of the effects of placental insufficiency with those of the inter-twin vascular connections, monochorionic pregnancies with similar degrees of fetal weight discordance may be associated with remarkable differences in clinical course and outcome. The identification of groups with similar clinical behavior may facilitate clinical management. To date, the clinical technique that best achieves this goal is umbilical artery (UA) Doppler of the IUGR twin.

A classification system of sIUGR is established into three types according to the umbilical artery Doppler patterns in the fetus with IUGR. Accordingly, pregnancies are defined as type I (normal umbilical artery Doppler), type II (persistent absent or reversed end-diastolic flow, AREDF) or type III (intermittently absent or reversed end-diastolic flow, iARED). This classification may help to understand and predict the distinct clinical evolutions and to plan clinical management of the different clinical forms of sIUGR (Valsky et al, 2010).

4.2.3.1 Type I sIUGR

The type I Doppler pattern is distinguished by positive diastolic flow in the umbilical artery of the small twin.

Types I cases are generally associated with good outcomes with intrauterine mortality rates of 2-4% (Gratacos et al, 2007). As clinical evolution of sIUGR type I cases has been shown to be benign in most cases, a policy of expectant management and close follow-up to rule out progression to type II Doppler patterns seems reasonable. In the absence of such progression, bi-weekly sonographic and Doppler surveillance could be proposed. In most cases, the IUGR fetus will remain with a normal Doppler until advanced stages of pregnancy allowing elective delivery, which can be performed at around 34-35 weeks (Valsky et al, 2010).

4.2.3.2 Type II sIUGR

Type II pattern is characterized by persistently absent or reversed end-diastolic flow (AREDF) in the umbilical artery.

Unlike type I, the great majority sIUGR type II will show in utero deterioration, but with important differences with respect to singletons or dichorionic twins. Type II sIUGR shows a remarkably longer latency time between the onset of AREDF and delivery, on average 10 weeks, compared with the 3-4 weeks reported in singletons with IUGR and similar findings in the UA Doppler (Vanderheyden et al, 2005). Severe fetal deterioration, as defined by abnormal venous Doppler or biophysical profile, will occur in the majority of type II cases (Gratacos et al, 2007). Elective delivery is indicated in most of these pregnancies earlier than 30 weeks of gestation (Gratacos et al, 2007) with only a small minority surviving in utero beyond 32 weeks. Thus, placental insufficiency in type II is far more severe than in type I and cannot be fully compensated by inter-twin transfusion. In 2007, Gratacos et al reported the outcome of 30 type II pregnancies, showing an extremely high deterioration rate (90%), as defined by abnormal venous Dopplers or biophysical profile. Mean gestational age at delivery was 30 weeks and the rate of neonatal brain damage of the small twin was 15%. In 2009, Ishii et al reported the outcome of 27 type II pregnancies. Intrauterine death occurred in 30% among IUGR twins and 22% among larger twins. The rate of neonatal brain damage of the small twin at 6 months was 15%. Mean gestational age at delivery was 28 weeks. The latency time between diagnosis of AREDF and fetal deterioration may be long and UA Doppler cannot be used as a predictor of imminent fetal death. The abnormal ductus venosus defined by absent or reversed atrial flow can be used as a criterion suggesting imminent fetal demise and indicating selective feticide or delivery to prevent the occurrence of in utero death (Gratacos et al, 2007). A weekly follow-up scheme may be reasonable if venous Doppler is normal, and a more frequent follow-up when venous Doppler pulsatility index becomes abnormal. Biophysical profile can be included in the follow-up protocol after viability is reached. Management options depend on gestational age and the severity of growth restriction. Fetal therapy should be contemplated to protect the larger twin from the death of its co-twin if deterioration occurs before viability is reached. Cord occlusion is the most straightforward and less risky procedure (Valsky et al, 2010).

4.2.3.3 Type III sIUGR

Type III is defined by the presence of intermittent absent or reversed end-diastolic flow (iAREDF) in the umbilical artery Doppler of the IUGR twin. The characteristic feature of this Doppler pattern is the alternation of phases of positive with phases of absent or reversed diastolic flow, normally but not always in a cyclical fashion. The observation of this sign indicates the presence of a large placental arterio-arterial (AA) anastomosis (Gratacos et al, 2004).

Contrary to type I cases these pregnancies are associated with a significant increase in the risk of unexpected intrauterine fetal demise of the IUGR fetus and of brain injury in the normally grown twin. These adverse outcomes are explained by the high risk of acute feto-fetal hemorrhagic accidents through the large AA vessel, which may lead to death of the smaller twin or acute hypovolemia in the larger one. Such acute feto-fetal transfusion may occur in the presence of short episode of bradycardia or hypotension in the smaller twin, and are facilitated by the large diameter of the AA anastomosis, which facilitates direct and rapid transfusion over a period of seconds (Valsky et al, 2010).

The majority of type III IUGR fetuses progresses until 32 weeks or later without abnormal venous Doppler or biophysical profile changes suggestive of fetal deterioration. In spite of this apparently benign evolution, 15% of IUGR fetuses die unexpectedly hours or days after a normal examination. In addition, even if both twins are alive, the larger twin had a significantly increased incidence (19%) of abnormal neonatal brain scans (Valsky et al, 2010).

Management of type III sIUGR represents a challenge (Valsky et al, 2010). Left to its natural evolution the prognosis would be better than in type II cases, but clinical decisions are more difficult due to the unpredictability of adverse outcomes. If expectant management is chosen, follow-up schemes should be similar to these discussed for type II cases; weekly follow-up if venous Doppler is normal, and closer follow-up with consideration of active management if venous Doppler becomes abnormal. Unfortunately, in type III the IUGR fetus will rarely show signs of fetal deterioration in venous Doppler, and therefore one reasonable option may be to deliver electively around 32 weeks of gestation. The reasons are similar to those used for decisions in monoamniotic pregnancies: to reduce the opportunity for unexpected adverse outcomes to occur. Type III pregnancies with milder forms of intermittent absent end-diastolic flow and moderate EFW discordance could probably be prolonged until 34 weeks. In case fetal therapy is considered, cord occlusion is a straightforward treatment. It seems reasonable that this therapy should normally be reserved for cases with extreme forms of iAREDF and/or extreme EFW discordance, or if fetal deterioration of the IUGR fetus is observed.

4.2.4 Twin reversed arterial perfusion (TRAP) sequence

TRAP is an abnormality unique to monochorionic twins with an estimated prevalence of approximately 1 in 35.000 pregnancies. In TRAP, the acardiac twin is a true parasite receiving blood from the pump twin through an arterioarterial anastomosis. The condition is associated with a high risk of perinatal death of the pump twin caused by a combination of high-output cardiac failure and polyhydramnios-related preterm birth (Moore et al, 1990).

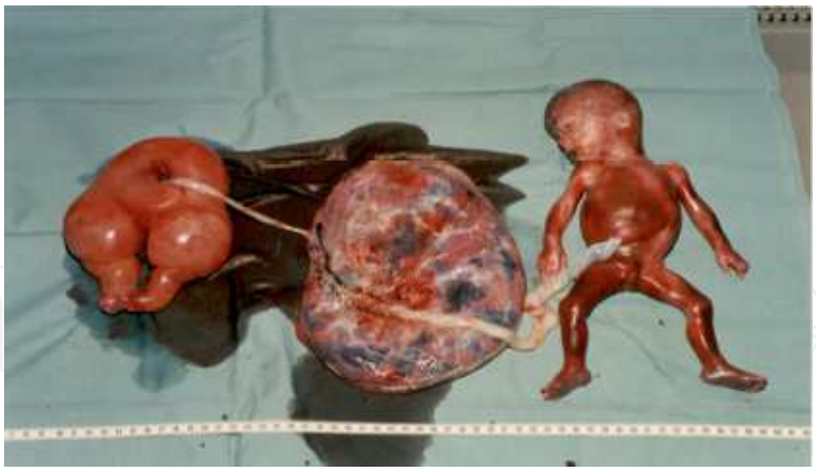

Fig. 4. Monochorionic twins pregnancy complicated by TRAP sequence.

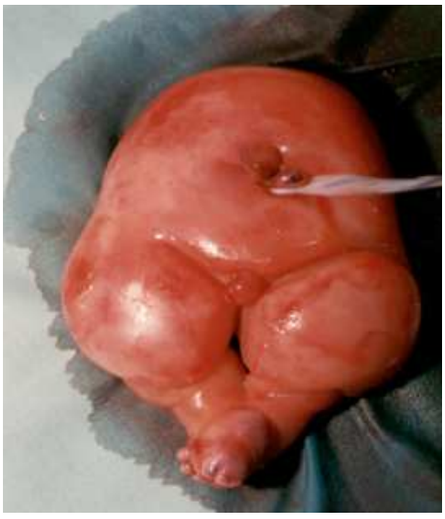

Fig. 5. Acardiac twin in a TRAP sequence.

The outcome may be improved by intrauterine intervention to arrest the circulation of the acardiac twin, as described below. In 33% of pregnancies, spontaneous death of the pump twin occurs between diagnosis and planned intervention. In 21%, there is a spontaneous arrest of flow (Lewi et al, 2010).

4.2.5 Monoamniotic twins

Monochorionic monoamniotic twins represents approximately 1% of all monozygous twins (Dickinson et al, 2005). Monoamniotic twins are the result of ovum division beyond 8 days postconception and are characterized by a single amnion and a single yolk sac. There may be two or one (conjoined twins) embryos present.

4.2.5.1 Conjoined twins

Conjoined twinning arises when the twinning event occurs at about 13-14 days after fertilization. Conjoined twinning occurs by the incomplete splitting of the embryonic axis.

Conjoined twins are typically classified by the point at which their bodies are joined. Management could be based on early assessment of fetal sharing by ultrasound and fetoscopy (Hubinont et al, 1997).

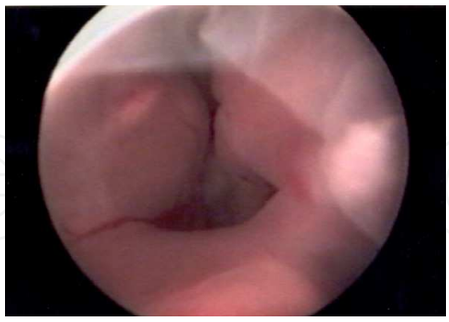

Fig. 6. Fetoscopic image of conjoined twins (Hubinont et al, 1997).

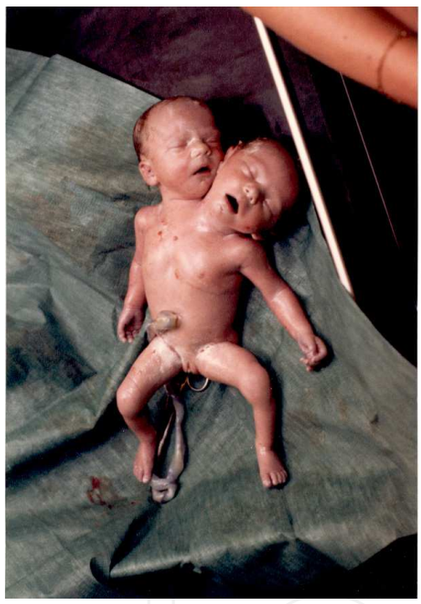

Fig. 7. Dicephalus: unusual case of conjoined twins (Hubinont et al, 1984).

4.2.5.2 Cord entanglement in monoamniotic twins

In monoamniotic twins, the high perinatal mortality rates have been attributed mainly to umbilical cord entanglement, intertwin transfusion syndromes, discordant fetal abnormality or growth restriction. Fetal demise because of umbilical cord entanglement and secondary cord occlusion is a unique characteristic of monoamniotic twin pregnancies. Umbilical cord entanglement is present in the great majority of monoamniotic twin pregnancies and may result in dual or single fetal demise. Umbilical cord entanglement may be detected with prenatal ultrasound and color Doppler. The initiation of cord entanglement can occur as early as first trimester, when the amniotic fluid volume in relation to the fetal mass is greater (Arabin et al 1999). In the literature, many strategies have been proposed including admission to hospital – after viability has been established – with cardiotocography several times a day and the use of pharmacological agents to reduce

amniotic fluid volume in the hope of preventing fetal loss from cord accidents. Intensive cardiotocographic monitoring may prevent some fetal deaths, but it is not surprising that it does not prevent all intrauterine death, as cord accidents can occur acutely without prior warning. Medical amnioreduction with sulindac, a non-selective prostaglandine synthase inhibitor used to treat preterm labor and polyhydramnios, was described to prevent the accumulation of a relative abundance of amniotic fluid that would otherwise allow unrestricted fetal movements and changes in fetal position, which contribute to the high intrauterine death rate from cord entanglement, compression and/or tightening of cord knots (Pasquini et al, 2006).

The cumulative rates of cord entanglement and perinatal mortality in the recent literature are 74% and 21% respectively (Table 1).

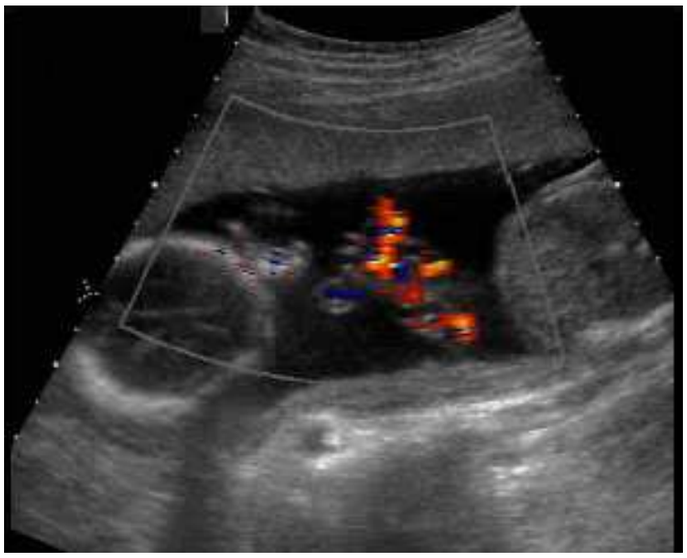

Fig. 8. Ultrasound image and color Doppler showing umbilical cord entanglement in a monoamniotic twin pregnancy.

Reference	Number of cases	Cord entanglement (n(%))	Intrauterine death (n)	Survivors (n)	Perinatal survival rate (%)
Sau et al. 2003	7	4 (57)	5	9	64
Ezra el al. 2005	30	26 (87)	24	35	58
Cordero et al. 2006	36	15 (42)	1	66	92
Pasquini et al. 2006	20	19 (95)	0	40	100
Hack et al. 2009	98	Not reported	34	150	77
Dias et al. 2010	18	18 (100)	2	32	89
Total	209	82/111 (74)		332/418	79

Table 2. Review of the published literature since 2000 indicating prevalence of cord entanglement and perinatal outcome (Dias et al, 2010).

4.3 Management of a twin pregnancy after in utero death

Single fetal death in a twin pregnancy is known to be a serious complication of pregnancy. It is a relatively rare complication of multiple pregnancies (6,2% of all twin pregnancies, Hillman et al, 2010) but may carry with its increased risk of perinatal morbidity and mortality.

Single intrauterine death can lead to adverse outcomes on the surviving co-twins, especially in monochorionic pregnancies. Co-twin death, neurological damage and preterm delivery have been reported as potential complications of these pregnancies. Surviving twins of dichorionic pregnancies develop fewer complications mainly due to prematurity, whereas those of monochorionic twins sets are also at greater risk of perinatal death or significant sequelae. In monochorionic pregnancies, placental anastomoses account for the poor outcome of the surviving twin (Ong et al, 2006). Two theories have been advanced to explain severe sequelae and co-twin death in these pregnancies. The first is that there is passage of thrombotic materiel from the dead to healthy twin following derangement in coagulation due to the death of one twin (Benirschke et al, 1993). The second theory states that the placental anastomoses allow transfer of blood from the surviving twin to the dead co-twin giving rise to periods of hypoperfusion, hypotension and acute fetal anemia, resulting in neurological damage (Bajoria et al, 1997). If the hypovolemic episode is severe, the surviving twin may develop ischemic lesions in vital organs such as the brain and the kidneys or, in some cases, die from hypovolemic shock or parenchymal damage.

It has been suggested that the possible mechanism responsible for organ damages or death of monochorionic co-twins occur probably before or at the time of single death and no therapeutic strategies after the diagnosis of death have been clearly demonstrated to reduce the risks of adverse outcome (Fichera et al, 2009).

Current practice advocates an expectant approach by serial fetal ultrasound and cerebral magnetic resonance imaging (MRI). An intensive surveillance in the 1-4 weeks following the diagnosis of intrauterine death is recommended to exclude cerebral lesions in utero and subsequent neurological sequelae in surviving monochorionic co-twins (Hillman et al, 2010).

Given this sequence of events in the death of monochorionic twins, conservative management has been advocated as the option of choice to avoid the risks of prematurity and therefore immediate delivery is an ineffective strategy to prevent co-twin damage (Nicolini et al, 1999).

A recent study (Fichera et al, 2009) confirmed the trend to an increased risk of perinatal mortality for the co-twin in case of single intrauterine death. This study reported a risk of co-twin death in utero of 16,5% for monochorionic pregnancies. A systematic review reported a risk of 18% of neurological sequelae in these cases (Ong et al, 2006).

5. Preconceptional prevention of multiple pregnancy related perinatal mortality

One of the priorities in the management of infertile couples remains the prevention of twin and higher-order multiple pregnancies in assisted reproductive techniques (ART). Attempts at reducing the incidence of higher-order multiples, such as triplets or more, have met with some success in countries that have legislated against multiple embryo reimplantations

during in vitro fertilization (IVF) cycles. However, even in these tightly controlled cycles twin pregnancies occur at a rate 10-fold that of normal cycle conception (Wimalasundera et al, 2003).

6. Antenatal prevention of multiple pregnancy related perinatal mortality

6.1 Selective termination of severely affected twin and multifetal pregnancy reduction

In the case of a discordant aneuploidy or an especially severe malformation of a twin, a selective feticide can be performed as early as the end of the first trimester. A multifetal pregnancy reduction can also be performed in patients with high-order multiple gestations in an effort to improve perinatal survival. Techniques should be chosen according to chorionicity.

6.1.1 Dichorionic twins

In dichorionic twins, selective pregnancy reduction or feticide are possible by potassium chloride intracardiac administration and do not present a direct risk to the healthy twin (Evans et al, 2004).

6.1.2 Monochorionic twins

In monochorionic pregnancies, a selective termination requires special considerations. The acute blood loss into the vascular anastomoses can cause death or severe neurologic impairment of the remaining unaffected twin. Selective feticide by umbilical cord occlusion is performed with bipolar forceps to prevent co-twin death and transfusional tissue injury. In the absence of imminent risk for the healthy twin, this procedure is recommended at or after 18 weeks. The risk of premature rupture of the membranes is approximately 20% and survival around 80% of the other twin (Vayssière et al, 2011).

Recent advances in vascular-occlusive techniques have allowed the possibility of selective termination in monochorionic pregnancies in the presence of discordant anomalies or multifetal reduction with radiofrequency ablation and cord occlusion appearing to be the most successful (Wimalasundera et al, 2010).

In early gestation intra-fetal techniques including interstitial laser and radiofrequency are used. Pregnancy loss and prematurity are the main risks of selective feticide and fetal reduction. Such complications have decreased as experience with the procedure has grown (Evans et al, 2005).

6.2 Invasive fetal therapy in monochorionic complications

TTTS is clinically characterized by an acute polyhydramnios (uterine distension, uterine contractions, dyspnea) causing maternal discomfort with an increased risk for preterm labor and premature rupture of the membranes.

6.2.1 Amnioreduction

One of the first treatments implemented for TTTS was serial therapeutic amnioreductions. The rationale for this technique is to prevent preterm labor related to polyhydramnios. It

was also hypothesized that amnioreduction may improve fetal hemodynamics by decreasing pressure on the placental surface vasculature (Elliott et al, 1991). Therapeutic amnioreduction has the great advantage to be a simple technique but has the disadvantage to require multiple procedures in the majority of cases (Hubinont et al, 2000).

6.2.2 Septostomy

Septostomy involves intentional puncture or rupture of the inter-twin septum and was first reported by our team on the occasion of a case that did improve following unintentional septostomy (Hubinont et al, 1996). The proposed mechanism of septostomy in TTTS is to equilibrate amniotic fluid pressure and maybe to provide available amniotic fluid around the donor and improve fetal hemodynamics. The main specific additional risk is the iatrogenic creation of a pseudo-monoamniotic twin pregnancy that can lead to cord entanglement. However, this may be reduced by performing a small hole just as in transeptal diagnostic amniocentesis in twins. Another potential risk of septostomy is to create floating amniotic membranes that could induce amniotic band syndrome (Hubinont et al, 2000).

Fig. 9. Fetoscopic image of intertwin septostomy in TTTS.

6.2.3 Laser coagulation

Fetoscopic (selective) laser coagulation of the placental vascular anastomoses is currently the best available treatment for TTTS diagnosed before 26 weeks. In the Eurofetus randomized controlled trial, Senat et al (2004) compared the safety and efficacy of laser surgery and amnioreduction in TTTS diagnosed between 15 and 26 weeks; endoscopic laser treatment resulted in a higher likelihood ratio of survival of at least one twin, and a smaller risk of neurological complications in the infant at 6 months of age. The risks of brain injury are reduced after fetoscopic placental laser but incompletely prevented in cases of incomplete coagulation of vascular anastomoses. Whereas previous data had shown a benefit of laser treatment only in foetuses with Stages 3 and 4, Senat also found a better outcome for fetuses with Stages 1 and 2. After 26 weeks, TTTS could be managed by amniodrainage, elective preterm delivery and in particularly sick twin by selective cord coagulation.

At the present time, amnioreduction is no longer the treatment of choice for pregnancies complicated by TTTS. It may still have a role in the management of TTTS under certain conditions. For example, to allow a patient to be transported to a center where laser may be offered, to decompress the uterus before a cerclage (in case of cervical shortening), to

manage symptomatic polyhydramnios when TTTS develops outside the gestational age when laser can be performed or when laser is technically not possible and finally, potentially, to manage stage I TTTS (Fichera et al, 2010).

It is important to recognize signs of TTTS early to improve the management of these pregnancies and diminish fetal loss and infant mortality rate among twins. Twice-monthly ultrasound monitoring, sometimes even weekly, is recommended for this type of pregnancy. TTTS is an obstetric emergency that is easy to diagnose with ultrasound. Treatment and counselling must be performed in a center that can offer fetoscopic laser coagulation of placental anastomoses. Monitoring after treatment should be conducted in association with the reference center. In the absence of complications after laser treatment, planned delivery is recommended from 34 weeks and no later than 37 weeks.

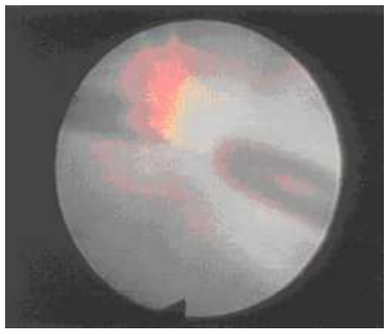

Fig. 10. Fetoscopic image of laser coagulation of the placental vascular anastomoses.

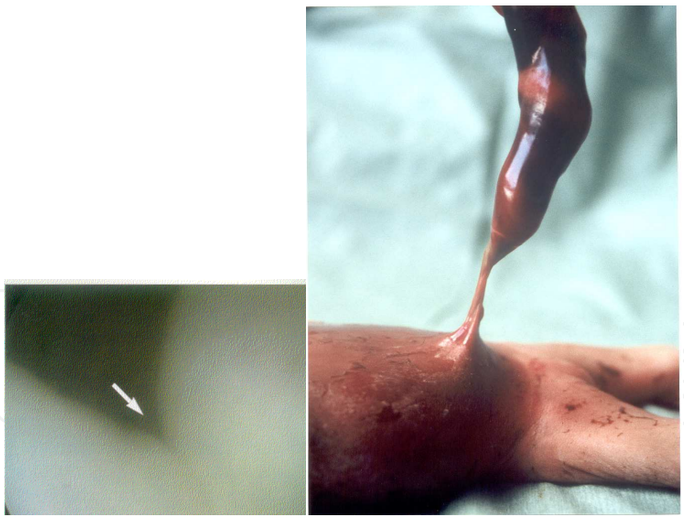

Fig. 11. Fetoscopic image of selective cord occlusion in a TTTS. Selective feticide by cord coagulation.

In twin reversed arterial perfusion (TRAP) sequence, the technique used to arrest the flow toward the acardiac twin consists of either ultrasound-guided intrafetal coagulation or fetoscopic laser coagulation of the umbilical cord and/or placental anastomoses. Intrafetal coagulation can be performed by using a radiofrequency needle (Livingston et al, 2007). Prophylactic surgery at 16-18 weeks seems to be the best option. Intrauterine interventions

are performed after 16 weeks (after obliteration of the celomic cavity) to reduce the risk of miscarriage. It seems preferable not to await signs of cardiac failure in the pump twin. Prophylactic intervention precludes the difficulty of achieving arrest of flow in the larger and often hydropic acardiac mass later on in pregnancy. In the patients undergoing prophylactic surgery at 16-18 weeks, 90% of infants survived and in 90% delivery was after 32 weeks (Lewi et al, 2010).

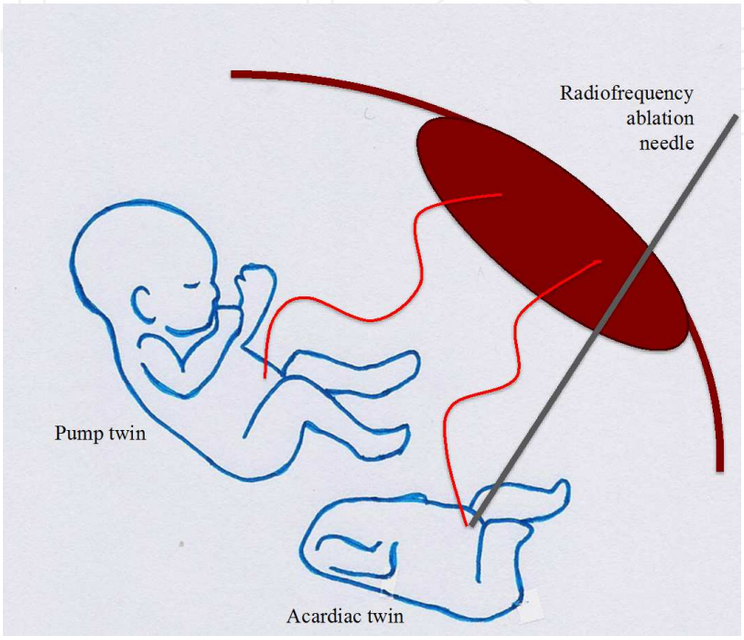

Fig. 12. Intrauterine intervention by radiofrequency ablation in a TRAP sequence.

6.3 Management of preterm birth

Considering the increased likelihood of preterm births among twin pregnancies, it is essential to determine whether it can be predicted. Transvaginal ultrasound measurement of cervical length and vaginal fetal fibronectin (fFN) level can be useful tool to differentiate those pregnancies that are likely to deliver prematurely. The rate of spontaneous preterm birth is significantly higher when either fFN is positive and/or cervical length is < 20 mm (Chauhan et al, 2010).

6.3.1 Tocolysis therapy

When preterm labour is diagnosed in twin pregnancies, its management should be done taking in account several factors such as maternal and fetal risks. The use of tocolytics for the treatment of preterm labour has not been shown to decrease the incidence of delivery within 7 days of treatment or perinatal death (Anotayanonth et al, 2004). The lack of proven efficacy, the high incidence of side-effects with some drugs such as adrenergic receptors agonists should be taken in account in the tocolysis guidelines for multiple gestations (ACOG, 2004). In Europe, atosiban and nifedipine seem to have the best balance between efficiency and side-effects profile. The role of progesterone should still be evaluated in randomized controlled trials (Dodd et al, 2008).

In contrast to tocolytics, the use of antenatal corticosteroids has been shown to decrease the incidence of neonatal death and others neonatal complications (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis) (Roberts et al, 2006). Tocolytic drugs should then aim to allow the pregnant patient transfer to a tertiary referral center or to ensure a proper antenatal corticosteroids course administration.

6.3.2 Cerclage

Another approach to decrease premature births could be to reinforce the cervix with a cerclage. The use of history-indicated (prophylactic) cerclage for twins gestation in a randomized trial did not decrease the rate of prematurity significantly (45% with cerclage vs. 48% without suture) or neonatal mortality (18% vs. 15% for suture vs. no suture, respectively) (Dor et al, 1982). More important, when cerclage was used in asymptomatic woman with twin gestations and short cervical length on transvaginal ultrasound examination, it significantly increased the risk of delivery at < 35 weeks of gestation (Berghella et al, 2005). Thus, cerclage of asymptomatic short cervical length should be avoided for twin gestations. Treatments that prevent preterm birth in singleton pregnancies, such as progesterone and cervical cerclage appear to be ineffective in multiple pregnancies (Stock et al, 2010).

6.4 Delayed twin delivery

One of the most common and serious complications of multiple gestations is preterm delivery. In some cases, preterm delivery of one fetus may occur without spontaneous delivery of the remaining fetus. This unique event raises the possibility of prolonging a pregnancy to a more advanced gestational age before delivery of the remaining fetus. The benefits of a delayed delivery can lead to a significant decrease in neonatal morbidity and mortality. During critical gestational ages, delayed delivery can also change the risk of delivering a periviable baby with severe morbidity related to prematurity instead of delivering a previable fetus. Attempts to delay delivery should only be undertaken in the absence of any maternal or fetal indications for delivery. Unfavorable conditions for delayed interval delivery are: monochorionic placentation, evidence of intrauterine infection, rupture of membranes of the retained fetus, placental abruption and fetal abnormalities. The gestational age at the time of delivery of the first fetus should be at least 16 to 18 weeks before prolonged interval delivery is considered (Farkouh et al, 2000). The conservative management of triplet pregnancy after delivery of one fetus is a feasible and reasonable approach and is not associated with significantly increased fetal-maternal morbidity (Biard et al, 2000). At the present time, the optimal management of a delayed delivery is not known, but immediate cerclage, broad-spectrum antibiotics, tocolysis and steroids for fetal lung maturity are a reasonable strategy (Graham et al, 2005).

7. Intrapartum prevention of multiple pregnancy related to perinatal mortality

7.1 Choice of delivery for uncomplicated twins

There is a general consensus that vaginal delivery for twins is safe when both are in vertex presentation, whereas planned caesarean section is typically indicated for breech presentation of the first twin.

A systematic review (Rossi et al, 2011) suggests that an attempt at vaginal delivery should be considered in twin pregnancies without inter-twin birth weight discordance (of more than 20%) and very low birth weight (< 1500g). Current literature shows that in twins with vertex/vertex presentation, vaginal delivery is safer than caesarean section for the first twin, and no differences are observed for the second twin after vaginal or caesarean section. In pregnancies with vertex presentation of the first twin and non-vertex presentation of the second twin, women should be counselled that trial of labour is a safe option in the absence of risk factors that may increase the risk of a caesarean delivery of the second twin after vaginal delivery of the first twin.

It is desirable for women with a twin pregnancy to have epidural analgesia. Vaginal delivery should be performed by an obstetrician with experience in the vaginal delivery of twins (Vayssière et al, 2007).

There is no reason to recommended one type of delivery rather than another in twin pregnancies, regardless of gestational age at birth. For both vertex/vertex and vertex/non-vertex presentations, morbidity and mortality are similar for vaginal and caesarean deliveries of twin gestations at or beyond 30 weeks of gestation and with birth weight twin greater than 1500 g (Peaceman et al, 2009).

At the present time, an international randomised controlled trial – the Twin Birth Study, coordinated by the University of Toronto – is underway. This study aims to provide more reliable information as to the optimal mode of delivery of uncomplicated twins. This study is in progress and the first results will be available in May 2012.

7.2 Delivery of the second twin

The systematic review (Rossi et al, 2011) describes a mild reduction of neonatal death occurred after vaginal delivery in both vertex and non-vertex presentation of the second twin as compared with caesarean section.

Active management of the delivery of the second twin is recommended to reduce the interval between the births of the two twins, because this interval is associated with:

- Progressive degradation of neonatal acid-base indicators,
- Increase in the number of caesareans for the second twin,
- Neonatal morbidity of the second twin,
- Obstetrical complications including placental abruption, umbilical cord prolapse, uterine atony and cervical spasm.

In the case of non-vertex presentation, total breech extraction, preceded by internal version manoeuvres if the twin's position is transverse, is associated with the lowest caesarean rates for second twins. In these situations, external cephalic version may be harmful. In the case of a high and not yet engaged cephalic presentation and if team is appropriately trained, version by internal manoeuvres followed by total breech extraction is to be preferred to a combination of resumption of pushing, oxytocin perfusion, and artificial rupture of the membranes, because the former strategy appears to be associated with fewer caesareans for the second twin. In the case of an engaged cephalic presentation, management should involve resumption of pushing, oxytocin perfusion, and artificial rupture of the membranes.

Obstetric manoeuvres on the second twin should be practised as first-line treatment with intact membranes (Vayssière et al, 2011).

A large dataset of twin deliveries (Peaceman et al, 2009) supports the safety of breech extraction for the non-vertex second twin, in contrast to studies of singleton breech vaginal deliveries, with their higher reported rates of morbidity and head entrapment. Perhaps this is because the larger twin usually delivers first, diminishing the chances that the cervix will be insufficiently dilated for the subsequent breech delivery.

7.3 Delivery of monochorionic pregnancies

7.3.1 Delivery of monochorionic diamniotic twins

A large cohort of monochorionic twin pregnancies without TTTS reported a risk of fetal death after 32 weeks of 5 in 1000 births and an incidence of perinatal mortality in term monochorionic twins of 7 per 1000 infants (Hack et al, 2011). This is three-fold higher than in term singletons and term dichorionic twin pregnancies. Unfortunately, current antenatal surveillance (i.e. fetal heart monitoring, fetal ultrasound and Doppler studies) fails to predict and prevent intrauterine fetal death. The increased risk of (unexpected) intrauterine fetal death (even at term), with subsequent consequences for the surviving twin (possible co-twin death or brain damage), and the failure to predict and prevent all cases of excess intrauterine fetal death by current antenatal care raise the question as to when to deliver monochorionic twins. Offering planned delivery between 36 and 37 weeks seems therefore to be the best consensus by preventing term mortality and avoiding the risk of neonatal respiratory disorders that is linked to preterm delivery (Escobar et al, 2006).

The contribution of mode of delivery to the increased perinatal mortality in monochorionic twins is not clear and there is no consensus regarding the optimal mode of delivery.

The monochorionic twins are more likely to have intrapartum complications as acute TTTS during labour. These complications may necessitate emergency caesarean delivery. Such complications could be prevented by offering planned caesarean section to all monochorionic twin pregnancies, as has been suggested in the literature (Smith et al, 2005). However, these benefits should be weighed against the risks of neonatal respiratory morbidity in infants delivered by planned caesarean section and maternal complications from the caesarean section.

There is a need for randomised data to determine the best strategy with respect to when and how to deliver the monochorionic twins.

7.3.2 Delivery of monochorionic monoamniotic twins

The timing of delivery in monoamniotic pregnancies is a balance between the risk of preterm birth and the risk of intrauterine death at a given gestation. The basis for timed elective delivery is to prevent cord-related deaths. Recent publication advocates delivery at 32-34 weeks gestation after corticosteroid maturation, when perinatal mortality rates in most neonatal intensive care units at gestations of 34 weeks are very low.

The majority of units use caesarean birth as the preferred delivery mode for monoamniotic twins. Caesarean delivery offers more control over complex events such as umbilical cord entanglement with difficulty in delivery of second twin (Dickinson et al, 2005).

8. Conclusion

Twins and higher-order multiple pregnancies are well known to carry a higher risk of adverse outcomes compared with singletons. Multiple pregnancies present numerous challenges for the obstetrician from conception onwards, until the timing and mode of delivery. The stillbirth rate in twins is four times and neonatal mortality is five to seven higher than in singletons (Anthony et al, 2009). The main cause of mortality is preterm birth and its short and long-term sequelae. Monochorionicity adverse effects, aneuploidy, congenital malformations, growth restriction, single fetal demise and delivery related problems are additional factors for increased perinatal mortality and should be diagnosed as soon as possible. A systematic ultrasound careful exam should be offered to these pregnancies (Hubinont et al, 2010). This chapter illustrates most of the complications of multiple pregnancies and the prevention of perinatal mortality. The higher risks have been shown in monochorionic pregnancies. All of these high-risk pregnancies require careful consideration with regard to the management of their specific complications in a maternal-fetal medicine center.

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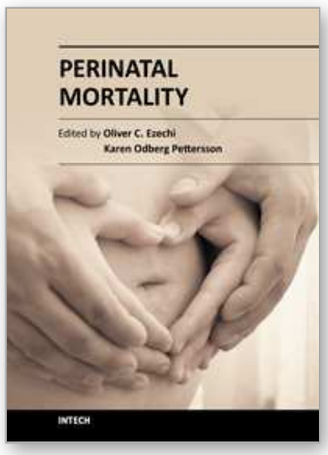

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This book is a compendium of important topics related to perinatal mortality. It has been written for anyone who is interested in perinatal medicine and wishes to be part of the global strategy for prevention and control of perinatal mortality. It covers variety of subjects using simple language that can easily be understood by most health workers and those interested in quality health care. Postgraduate students in midwifery, obstetrics and paediatrics will also find it a very useful companion.

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