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# Monochorionic Twin Pregnancy— Potential Risks and Perinatal Outcomes

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Gustavo Nardini Cecchino

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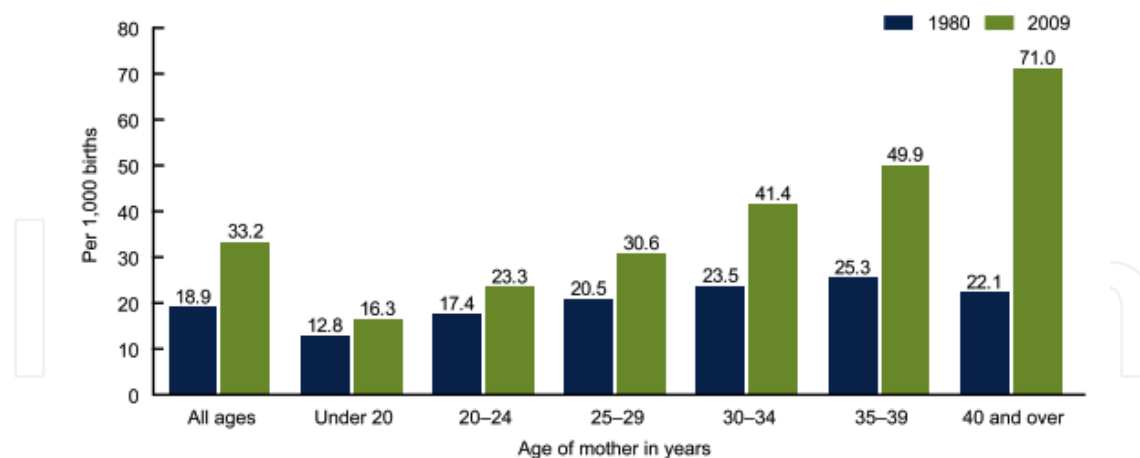
## 1. Introduction

Since the most ancient times, mythical stories concerning twins were described both in religion and art [1]. Examples of twin gods and heroes are numerous: from the twin sons of Zeus to Rome's founders, Romulus and Remus. Such legendary conception connected to twins may still be found in contemporary primitive societies [2]. The evolution of medicine has led to a different perception of the twinning phenomenon, with several implications for the obstetric care [3].

The frequency of multiple pregnancies has been increasing since the 1970s. Contributing factors include the wide use of fertility drugs and assisted reproductive technologies, along with a higher number of women giving birth at older ages [4]. Nevertheless, many physicians still underestimate the adversities of multiple pregnancies. [5].

## 2. Importance

The number of twins has doubled and the rate of twin births has risen from 18.9 to 33.2 per 1,000 births in the United States. Recent data brief from the National Center for Health Statistics states that one in every 30 infants born in 2009 was a twin. Twin birth rates increased in all US states from 1980 to 2009, mainly among non-Hispanic white mothers and women aged 40 and over, which demonstrated the largest increase by more than 200 percent as shown in Figure 1 [6].



Source: CDC/NCHS, National Vital Statistics System [6]

**Figure 1.** Twin birth rates, by age of mother. United States, 1980 and 2009.

A consistent growth in the number of multiple births in England has also been well documented [7]. Analysis from the North of England Multiple Pregnancy Register during 1998 and 2002 showed an increasing twinning rate of 13.6 to 16.6 per 1,000 maternities [8]. Similarly, secular changes in twinning rates were demonstrated by previous study, in which 15 out of 17 European countries listed significant increasing proportions between 1972 and 1996 [9]. Records from the Danish National Birth Cohort revealed an overall frequency of twin deliveries of 22 per 1000 [10].

Over the last 20 years in Japan, the incidence of twin births increased until 2003, when it started to decrease reaching similar rates to those registered in the 1990s [11]. The reported Chinese twinning rates range from 2.8 to 15.4 per 1000 births. This wide variation may be explained by the lack of systematic vital records [12]. Historically, the lowest twinning rates are registered in Asian countries (5–6 per 1000 maternities), and the highest rates are seen in Sub-Saharan-Africa (23 per 1000 maternities), notably Nigeria, with rates up to 40 per 1000 births [13].

The average rate of twin births in Brazil is 10 per 1000. Cândido Godói is a modest town in South Brazil universally known as “Twins’ Town”, considering its twinning rate of 2% and an estimated rate of 10% in the very small district of Linha São Pedro. It was hypothesized that such a high rate of twin births could be due to Nazi’s experiments commanded by Joseph Mengele in the 1960s. Recent data suggest that this phenomenon is much better explained by a genetic founder effect [14].

There is a global tendency of an increased number of multiple gestations, with the exception of triplets and higher-order multiple gestations [15]. This fact was largely attributed to an elevated amount of dizygotic pregnancies, without significant variations in monozygotic births over the past few decades [4]. The dizygotic twinning rate is affected by innumerable factors such as race, parental consanguinity, maternal age and parity, lifestyle, season, use of fertility drugs and treatments, genetics and others [4, 5, 12].

Currently, it is very difficult to estimate trends in spontaneous twinning regardless of the use of fertility treatments [4]. Assisted reproductive technology has played a major role in multiple birth rates, especially after the 1980s. Evidences indicate that 30-50% of twins and at least 75% of triplets occur after infertility treatment. Therefore, several physicians and reproductive medicine societies have recommended rigorous strategies for reducing the risk of multiple pregnancies, like single-embryo transfer [16].

### 3. Impact of multiple gestations

Multiple pregnancies are strongly associated with greater maternal morbidity. Studies demonstrate a maternal mortality risk as much as three times higher and the numbers of intensive care unit admissions are nearly twice as those in singleton [16]. Major obstetrics complications include: miscarriage, growth retardation, pre-eclampsia, gestational diabetes, caesarean section, preterm delivery and post-partum hemorrhage [17].

Multiple children are at increased lifetime risk of developing medical complications, mainly due to the extremely high rate of preterm delivery and low birth weight among twins. Of all factors contributing to perinatal mortality, preterm newborns alone account for 70%. Likewise, infants born with less than 2500g are almost 40 times more likely to die during early infancy [18, 19]. Population-based data show greater proportions of disabilities in twins compared to singleton, with up to 3 to 7-fold increase in cerebral palsy [5, 20]. Furthermore, twinning phenomenon is associated with a higher incidence of congenital anomalies, especially among monozygotic pregnancies [16, 20].

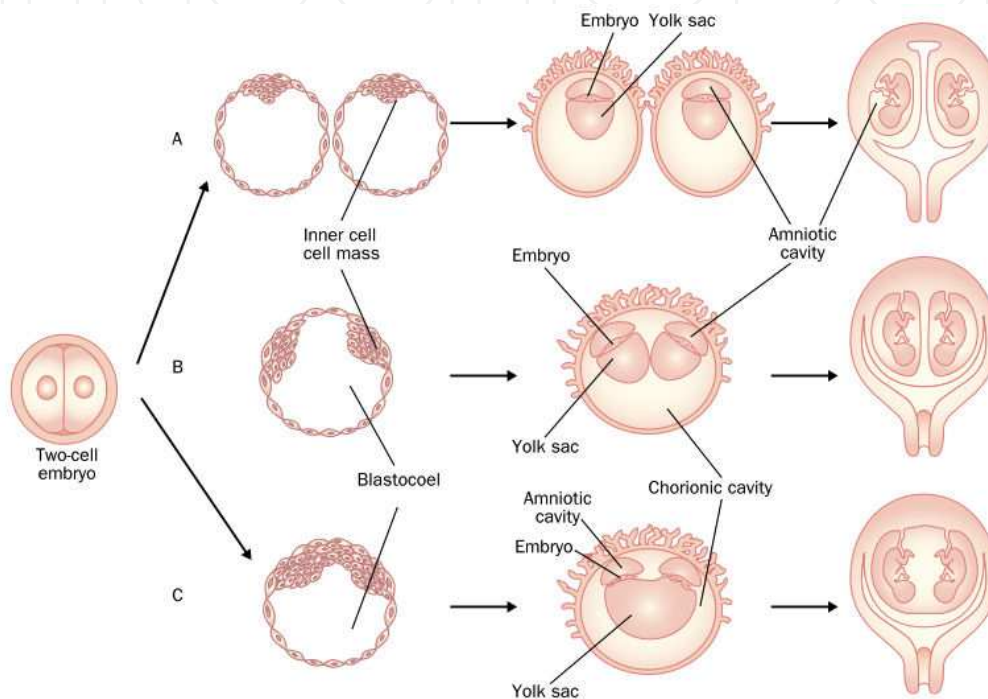
Becoming pregnant of more than one baby imposes supplementary social implications during the antenatal and the postnatal periods. Most parents exhibit feelings of shock and isolation, which may often lead to psychological consequences such as postnatal depression. Moreover, women carrying multiples are more likely to suffer with the severity of pregnancy symptoms. Also, myths and misunderstandings regarding multiples generate many issues that the maternity care provider should be prepared to explain. Lack of sleep and personal time, chronic stress, fatigue, exhaustion and financial strains are common dilemmas experienced by parents. Delayed development, attention deficit and learning difficulties usually affect multiple children, especially due to lack of sufficient one-to-one stimulation. The prevalence of disabilities is estimated to be at least 50% higher in twins and 100% in triplets [17, 20].

In addition to all negative consequences of multiples, economic implications should also be considered. The increase in multiple births defies the current trend to lower medical costs [19]. A large study conducted in the Brigham and Women's Hospital by Callahan et al. [21] showed that multiple pregnancies contribute to a dramatic rise in hospital charges. Total family charges for a 29-year-old white mother in 1991 was estimated to be US\$ 9, 845 for a singleton, compared to US\$ 37, 947 for a mother of twins and US\$ 109, 765 for higher-order multiple-gestation [21]. In large scale it could trigger a public health collapse.

## 4. Pathogenesis of twinning

### 4.1. Monozygotic gestation

One-egg twins result from a single fertilized oocyte. Depending on the spontaneous embryo preimplantation division at various stages of development into two genetically identical structures, three types of monozygotic pregnancies are distinguished according to Corner's embryologic theory as shown in Figure 2 [22]:



**Figure 2.** Three types of monozygotic placenta and membrane. A: dichorionic diamniotic. B: monochorionic diamniotic. C: monochorionic monoamniotic. From *The Lancet*, JudithGHall [23], with permission from the publisher.

- Dichorionic diamniotic if the division of the blastomeres occurs within 72 hours post-fertilization. The amnion and the chorion have not yet developed, resulting in two independent embryonic discs and diplacental monozygotic twins.
- Monochorionic diamniotic when the division of the blastocyst occurs between day 4 and day 7 post-fertilization. The chorion is already formed but not the amnion, culminating in monoplacental monozygotic twins.
- Monochorionic monoamniotic if the division of the embryoblast occurs after day 8 post-fertilization. The chorion and the amnion are fully grown, configuring monoplacental monozygotic twins as well. Even later division, usually after the 13<sup>th</sup> day, gives rise to conjoined twins, since the germ disc is completed.

The monozygotic twinning phenomenon happens in a proportion of 1:250 multiple pregnancies [5]. Usually, they share the same genetic and physical features; however, a simultaneous

chromosomal error may result in heterokaryotypic monozygotes, especially in very early splits [24]. Mothers originated from a monozygotic pregnancy have exceeding rates of monozygotic twins. Despite being relatively constant and independent of factors such as ethnicity, maternal age and parity, the occurrence of monozygotic twinning is increased with in vitro fertilization and ovarian stimulation [5].

#### 4.2. Dizygotic gestation

Two-egg twins result from simultaneous ovulation of two ova fertilized by two different spermatozoa. Thus, necessarily, two chorionic sacs are developed even in cases of fused placenta [25]. Both zygotes have different genetic constitutions, on average sharing 50% of their genes, and they can be of the same or opposite sexes [13]. Almost 75% are of the same sex, with both male twins in 45% of cases [24]. An excessive follicular recruitment occurs in 31% of mothers of dizygotic twins, who have greater basal follicle-stimulating hormone (FSH) concentration and pulse frequency, associated with elevated secretion of gonadotropin-releasing hormone (GnRH). These findings suggest that multiple ovulations are extragonadally determined [5].

Season is known to influence the dizygotic twinning process as well as the use of folic acid and oral contraceptives. Evidences suggest a slight tendency for dizygotic twins to be conceived at summer and autumn, which probably reflects the light's effect on pineal gland and the release of higher titles of FSH [5, 13]. A recent systematic review indicates a possible positive association between the use of periconceptional folic acid and increased twinning, but additional well-designed studies are needed [26]. Several researches showed raised risk for multiple pregnancies after discontinuation of oral contraceptives due to a temporary increase of FSH levels [27, 28].

Whether there is a recessive or dominant inheritance pattern for dizygotic twinning is still controversial. The fact is that a substantially greater female genetic contribution was observed, in contrast with limited evidence for a paternal effect [29, 30]. Genetic mutations could not yet be definitively associated as a cause of hereditary dizygotic twinning, but genetic mapping studies support a mechanism of inheritance connected to chromosomes 2, 7 and 18. Further investigations are needed [13].

#### 4.3. Other forms of multiple gestation

Superfecundation is the fertilization of two or more ova from the same ovulation cycle by sperm released at intercourse on different occasions, not necessarily from the same partner (heteropaternal superfecundation). Cases of twins with different fathers have been reported since 1940 by red cell antigen typing, and these findings were later endorsed by human leukocyte antigen (HLA) typing [31, 32]. Genetic disease studies and circumstances of disputed paternities allowed more accurate diagnosis [33]. Recently, a case of heteropaternal superfecundation was reported in a pair of Danish twins [34].

Superfetation is the fertilization of 2 ova released in different menstrual cycles, resulting in the onset of a subsequent pregnancy during an ongoing pregnancy. The occurrence is more rare

than superfecundation and only few human cases have been described [35]. Confirmation requires ultrasound scanning during the first trimester, but neurosonography with detailed ophthalmic examination may support the diagnosis. Superfetation has innumerable antenatal implications although it is very difficult to retrospectively confirm the diagnosis postnatally [36]. Considering the absence of substantial evidence, we believe the superfetation mechanism could only be possible in theory.

## 5. Diagnosis of chorionicity

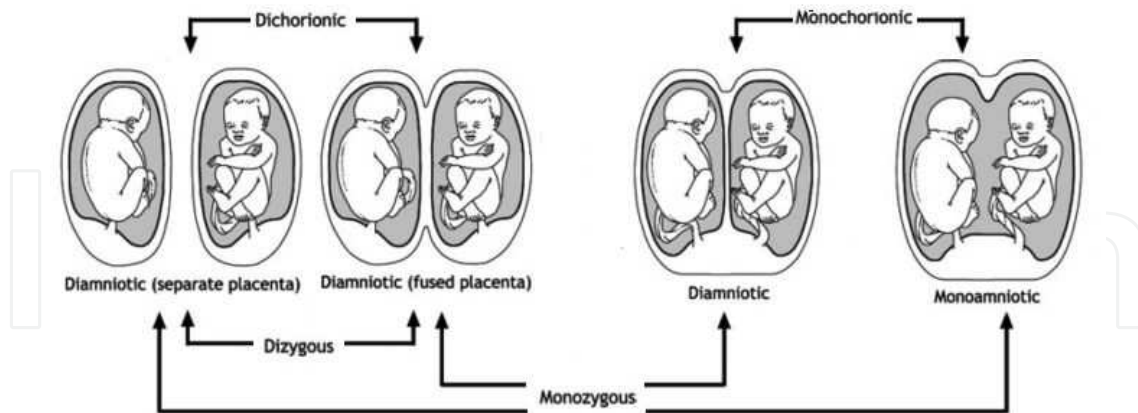
Chorionicity, different from zygosity, refers to the type of placentation and it directly impacts obstetric management (Figure 3) [37]. Distinguishing the placental chorionicity plays a critical role in clinical practice since perinatal mortality rates are 2-5 times higher in cases of monochorionicity, which is present in 20% of all twin pregnancies [37, 38]. Monochorionic placentas may present vascular communications that can induce several syndromes. These vascular anastomoses also explain the existence of chimerism and mosaicism upon monozygotic twins [23].

Correct antenatal assignment of chorionicity is very important not only for risk stratification and prenatal monitoring, but also for genetic counseling, invasive procedures, diagnosis of twin-twin transfusion syndrome (TTTS) and growth abnormalities, as well as for the management of conditions affecting only one twin [39, 40]. Thus, the ascertainment of chorionicity has enabled the prevention of undesired repercussions.

Currently, early sonographic study is the gold standard for the antenatal twin chorionicity prediction. When assessed before 14 weeks' gestation it is extremely precise, with reported accuracy rates ranging from 77 to 100% [40, 41]. Such large variation can be mainly explained by the use of different ultrasound markers and by the time of scanning. Combining first-trimester sonographic parameters makes it possible to reach accuracy close to 100% [41, 42].

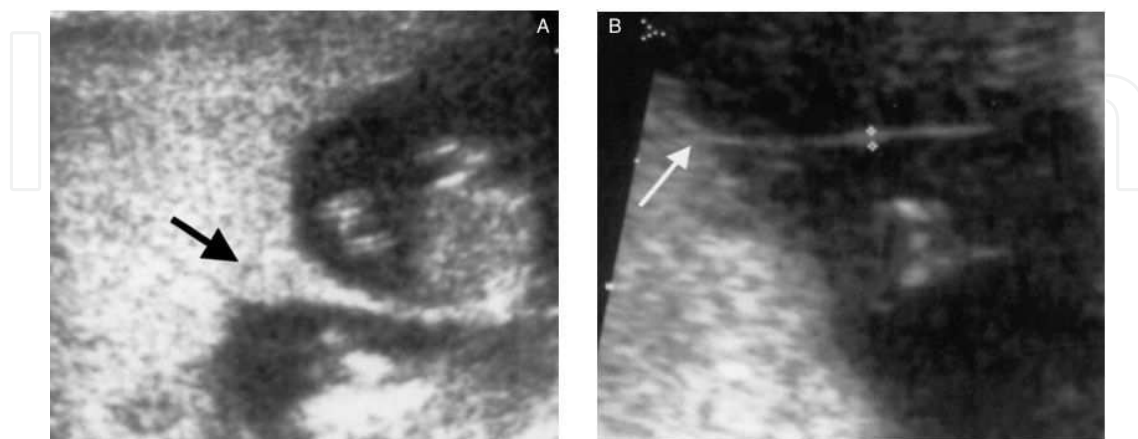
The identification of two clearly separate placentas or gestational sacs during the earliest first-trimester ultrasound scanning indicates dichorionic twinning, with more than 97% sensibility and 100% specificity. In cases of single or even fused placenta, the chorionicity can be assessed either by the presence of lambda sign or T-sign (Figure 4). Measurement of the inter-twin membrane thickness and counting of the layers of the inter-twin membrane are less useful indicators [37, 42].

In 1981, Bessis and Papiernik [43] first described the lambda sign as a reference for the triangular projection of placental tissue observed at the base of the inter-twin membrane in cases of dichorionic placentation. It has been mutually used with the twin peak sign, described later in 1992 by Finberg [44]. The lambda-sign is better perceived in the late first and early second trimester ultrasound scanning, and may disappear by week 20 in 7% of dichorionic pregnancies with fused placenta [41, 42]. The absence of twin peak sign neither excludes dichorionic pregnancy nor implies monochorionicity [37].



**Figure 3.** Different patterns of placentation for twins. Adapted from *Prenatal Diagnosis, Shetty&Smith* [37], with permission from the publisher.

The T-sign has been traditionally used to describe the point where the two opposing amnions at the base of the separating membrane approach the placenta at almost a 90° angle, characterizing a monochorionic placentation [37, 42]. In 2002, Carroll et al [38] performed the very first robust study evaluating sonographic signs between 10-14 weeks of gestation. In their series of 150 cases, the prenatal chorionicity diagnosis was confirmed postnatally by placental histology. They identified a sensitivity and specificity of the T-sign in predicting monochorionicity of 100% and 98.2%, respectively. The combination of the lambda sign or two separate placentas showed a sensitivity of 97.4% and specificity of 100% to predict dichorionicity. Innumerable studies were subsequently carried out and similar sensitivity and specificity percentages were reported [41].



**Figure 4.** First trimester ultrasound image of a fused dichorionic placenta with lambda sign (A) and first trimester ultrasound image of a monochorionic placenta with T sign (B). Adapted from *BJOG, Carroll et al.* [38], with permission from the publisher.



The antenatal chorionicity determination is remarkably precise. Yet, eventual mistakes have a major impact on patient counseling, pregnancy monitoring and perinatal outcome. Some researchers are going for 3-D ultrasound but its contribution for chorionicity determinations is still unclear. Further studies should be encouraged [39, 40].

Recognition of zygosity is more difficult to be predicted and can be either performed by ultrasound or noninvasive molecular genetic tests. Only 55-65% of twin pregnancies zygosity can be determined by correlating chorion type with the sex of twins [45, 46]. Invasive approaches combined with microsatellite DNA markers could also detect zygosity, but they have the inconvenience of a miscarriage risk of 0.5-1%. Recently, Zheng et al [47] developed a noninvasive method based on maternal plasma target region sequencing through a bioinformatics' model with promising results.

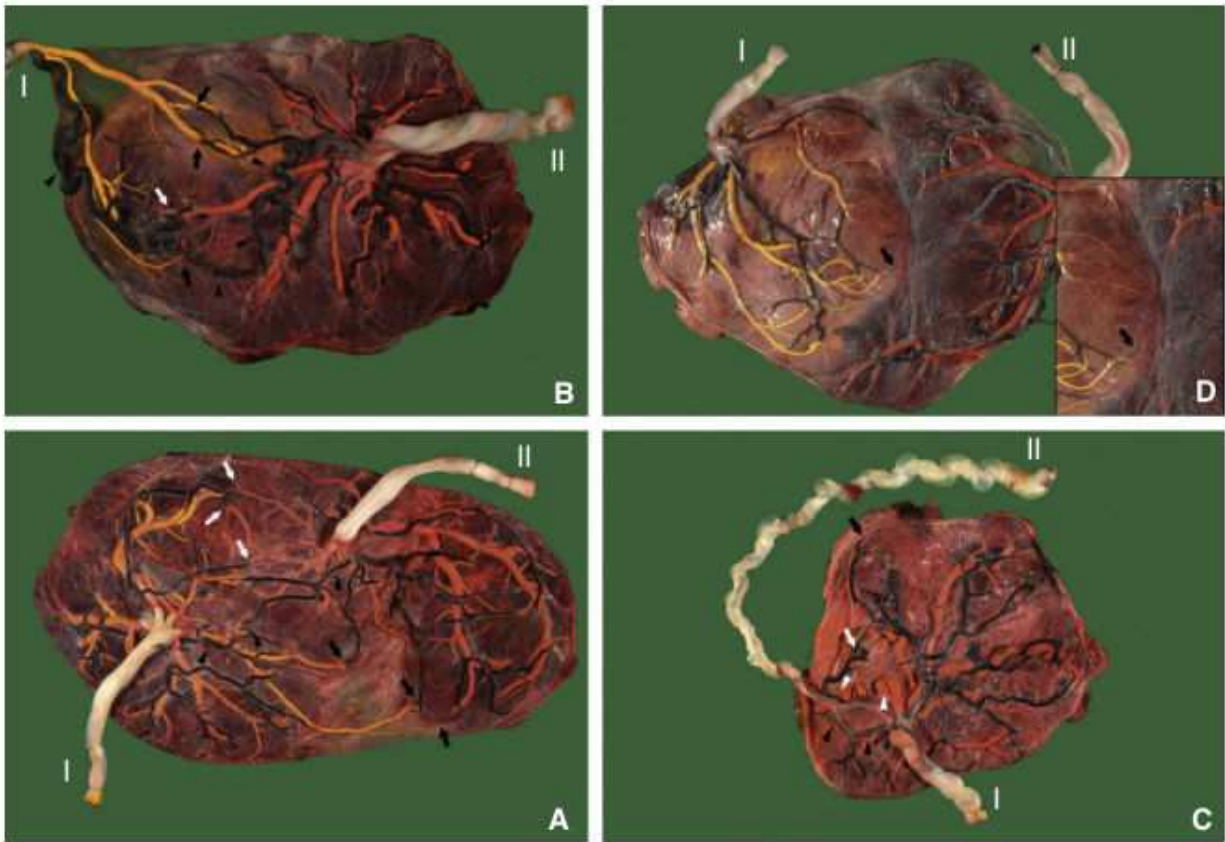
## 6. Placental characteristics in monochorionic twins

Monochorionic placentation is associated with higher perinatal morbidity and mortality as a result of placental morphologic characteristics and vascular problems (Figure 5) [48]. Overall, almost 1% of all monozygotic twin gestations are monoamniotic, which consist of both single amniotic cavity and placenta, sharing two umbilical cord insertions. This may lead to a complication specific to monoamniotic twins: cords entanglement and knotting [49]. For decades it was believed that cord entanglement was responsible for most fetal deaths, but recent studies, including a systematic review, showed no contribution of cord entanglement to prenatal morbidity and mortality [50, 51].

Superficial vascular anastomoses are present in all monoamniotic placentas, with the majority being of arterioarterial and arteriovenous type. Also, a small distance between cords' insertion are observed in most cases, as well as a low incidence of velamentous cord insertion (4%). No significant association among various morphologic or histopathologic characteristics of monochorionic monoamniotic placentas and perinatal mortality were reported. Furthermore, no relation between severe birth weight discordance ( $\geq 20\%$ ) and unequally shared placenta or velamentous cord insertion were described. Twin-twin transfusion syndrome is a rare condition in monochorionic monoamniotic placentas due to the protector effect of the arterioarterial anastomoses [49, 52].

Likewise, monochorionic diamniotic placentas did not demonstrate a clear relation between placental angioarchitecture, intercord distance and shared placental territories with greater perinatal mortality. Twins with unequally shared placentas and velamentous cord insertion significantly lower mean birth weight. Perinatal mortality was found to be substantially higher in the presence of velamentous cord insertion [48].

Additionally, in cases of TTTS, vascular anastomoses are more likely to be of deep other than superficial type. Most anastomoses are arteriovenous, and vascular communications are fewer in number without compensating superficial arterioarterial flow [53]. Moreover, evidences suggest that unequally shared placentas and velamentous cord insertion are not mandatory for the occurrence of TTTS [54].



**Figure 5.** Monochorionic placentas after injection with coloured dye. The veins are coloured yellow or orange and the arteries are black or blue. The white arrows indicate arteriovenous anastomoses from twin I towards twin II; the black arrows indicate arteriovenous anastomoses from twin II towards twin I. The white arrowheads indicate venovenous anastomoses and the black arrowheads indicate arterioarterial anastomoses. **(A)** Placenta of monochorionic twin without TTTS, delivered at 36<sup>+6</sup> weeks of gestation. Similar placental territory for both twins. **(B)** Placenta of monochorionic twin with selective intrauterine growth restriction. Caesarean section at 32 weeks of gestation after determination of lung maturity. The growth-restricted twin I has a velamentous cord insertion and placental territory of 28%. **(C)** Placenta of monochorionic twin with mild TTTS. Caesarean section at 32 weeks of gestation due to TTTS. The recipient twin I has a placental territory of 82%. **(D)** Placenta of monochorionic twin with TTTS, conservative management. Caesarean section at 31<sup>+5</sup> weeks for signs of anemia in the donor twin. Adapted from *Placenta*, Hack *et al.* [48], with permission from the publisher.

## 7. Antenatal care in monochorionic pregnancies

Multiple pregnancies impose a higher risk of complications for both mother and baby; therefore, adverse outcomes take place more often [55]. Intensive antenatal care should be provided along with a multidisciplinary team. Furthermore, an effective interpersonal communication between healthcare professionals and women is fundamental [56].

The very first step for quality assistance is an early detection of multiple pregnancies along with appropriate amnionicity and chorionicity determination as soon as possible. Whenever the diagnosis of chorionicity is uncertain, the woman should be referred to a specialist or a senior ultrasonographer before 14 weeks. If still indeterminate, even after referral, the pregnancy should be managed as monochorionic until proven otherwise [55-57]. Parents should be thoroughly informed about the implications of a monochorionic pregnancy [58].

Nuchal translucency should be offered as a screening for fetal aneuploidies. The detection accuracy is better when combining maternal age, nuchal fold, crown-rump length, and serum markers [42, 55]. Some professionals do not recommend the routine use of serum markers neither in the first trimester nor during the second trimester [59], while others do recommend for both situations [56].

The prevalence of congenital anomalies is almost twice when comparing monochorionic twins with dichorionic, although in both cases only one fetus is affected in 90% of the time. In case of a suspicious screening exam, a fetal echocardiographic assessment should be considered. The same applies for in vitro fertilization conceived twins and cases of severe TTTS [42]. First trimester surveillance for TTTS is not advised [55, 56, 58]. When applicable, chorionic villus sampling is preferred over amniocentesis and the transabdominal route is the best choice [59].

Placental evaluation and cervical length assessment are also important. Placenta previa is 40% more common in twins, and so is vasa previa. The placental cord insertion should be determined once velamentous cord insertion is associated with greater risk of TTTS, unequal placental sharing and perinatal mortality. Cervical length smaller than 20-25 mm raises the likelihood of preterm delivery in 3-5 times [42].

Serial sonographic monitoring for intrauterine growth restriction (IUGR) or discordance is warranted rather than abdominal palpation, symphysis-fundal height measurement or umbilical artery Doppler [42, 55, 56]. Only an estimated fetal weight discordance greater than 25% is clinically important [55, 56]. Both IUGR and twin discordance are associated with increased risk for fetal and perinatal death [42]. A recent prospective cohort study showed that twin birth weight discordance might be predicted with an abdominal circumference ratio cutoff of 0.93, with a sensitivity and specificity of 61% and 84%, respectively [60].

Additionally, it is also mandatory to monitor for maternal complications, especially for hypertensive disorders that present an increased likelihood of 2 to 3-fold. Concerning gestational diabetes, whether its occurrence is increased or not is still controversial. The management of all maternal complications shall not be different from singleton pregnancies [55].

Table 1 shows an overview of ultrasound applications for twin pregnancies [42]. Monthly prenatal consultations are strongly recommended for all monochorionic pregnancies, as well as ultrasound scanning every 4 weeks for uncomplicated dichorionic pregnancy and every 2 weeks for uncomplicated monochorionic twins [42, 59].

Indication	Timing	Comment
Pregnancy dating	First trimester	Optimal at 7–10 weeks using CRL
Determination of chorionicity	First trimester	Close to 100% accuracy if done prior to second trimester
Nuchal translucency assessment	10–13 weeks	Increased with aneuploidy, malformations, TTTS
Anatomical survey	Second trimester	Optimal at 18–22 weeks; fetal echocardiography for IVF twins and/or monochorionic twins
Placental evaluation	Second trimester	Transvaginal imaging to exclude previa and vasa previa; color imaging for PCI
Baseline cervical length	Second trimester	Transvaginal imaging optimal
Twin growth studies	Second and third trimester	Every 4 weeks for uncomplicated twins
Serial surveillance	Second and third trimester	Every 2 weeks for uncomplicated monochorionic twins; daily testing at viability for monoamniotic twins; frequency and type of testing of twins depends on chorionicity, risk, and complications

CRL = crown–rump length; TTTS = twin–twin transfusion syndrome; IVF = in vitro fertilization; PCI = placental cord insertion.

From Seminars in Perinatology, Lynn Simpson [42], with permission from the publisher.

**Table 1.** Ultrasound in twins

## 8. Antenatal complications

Certainly, preterm birth is the most relevant complication related to multiple pregnancies. Current available data in the literature are insufficient to determine effective preventive strategies, limiting the applicability of routine screening methods to predict preterm delivery [55].

Two recent systematic reviews and meta-analysis concerning the use of transvaginal sonographic cervical length to predict spontaneous preterm birth in twin pregnancies concluded that women with a short cervix are at increased risk [61, 62]. Testing for fetal fibronectin should not be used as a single approach to suppose a greater risk of preterm delivery in twins. If combined with cervical length measurement it might be valuable [55, 56]. Also, women with a history of previous preterm singleton delivery are at increased risk of preterm birth in a subsequent twin pregnancy [63].

All studied interventions to prevent spontaneous preterm labour in twin pregnancies up to date failed, including hospitalization and bed rest, progesterone treatment, prophylactic cervical cerclage or pessary and the use of betamimetics [64–69]. This is the rationale for worldwide guidelines to discourage any of the above-mentioned strategies [56, 59, 70]. Further well-designed, properly powered, prospective randomized trials are warranted prior to widespread implementation in clinical practice.

It is well known that both antenatal corticosteroids and magnesium sulphate reduce neonatal complications in preterm babies related to lung maturity and neurological development respectively, regardless of fetal number [71, 72]. Although, there is no evidence to support neither the routine use of untargeted course of steroids nor magnesium sulphate therapy, except when preterm labour or birth is imminent [55, 56, 70].

Other antenatal complications, including those specific to monochorionic twins, were exhaustively discussed along the chapter.

## 9. Monochorionic twin pregnancies specific complications

### 9.1. Twin-Twin Transfusion Syndrome (TTTS)

Chronic twin-to-twin transfusion syndrome is a specific complication of monochorionic pregnancies, almost exclusively to monochorionic diamniotic placentation. It results from an unbalanced unidirectional blood flow through placental arteriovenous anastomoses, and the proportion is up to 15% of all monochorionic pregnancies [73]. Additional factors such as vasoactive hormones are also believed to influence the development of TTTS [74].

Commonly diagnosed during routine second-trimester ultrasound scanning, its predicted peak in incidence is around 20-21 weeks of gestation [75]. The presentation is highly variable and the recipient twin may present circulatory overload and polycythemia, possibly leading to congestive heart failure and hydrops. Contrarily, the donor twin shows oliguria and oligohydramnios, as well as anemia and growth restriction. Acute unbalancement can also occur at any time before birth, threatening the prognosis [76].

Data shows that 17% of the overall twin's perinatal mortality and 50% of all perinatal deaths in monochorionic diamniotic twins are attributed for TTTS [77].

### 9.2. Diagnostic criteria

TTTS is properly diagnosed after confirmation of monochorionic twin pregnancy in early sonography demonstrating T-sign. In late diagnosed cases, chorionicity is supposed when single placental mass and a thin intertwin membrane are seen [78]. Besides the confirmation of a monochorionic diamniotic gestation, the presence of oligohydramnios (maximal vertical pocket <2 cm) within the donor sac, instead of polyhydramnios (maximal vertical pocket >8 cm) in the recipient sac are also essential [74, 77]. Differential diagnoses include selective intrauterine growth restriction and other causes of amniotic fluid abnormalities [77].

Additional sonographic findings usually coexist with TTTS such as significant growth discordance, absent or reversed a-wave in the ductus venous and velamentous cord insertion [74]. TTTS frequently occurs acutely and a meticulous follow-up in a specialized center is strongly recommended. The initial ultrasound assessment should include detailed anatomy scan and Doppler study, along with cervical length measurement. Fetal echocardiography is a valuable option for cardiac function evaluation [75].

### 9.3. Severity staging

In cases of sudden TTTS aggravation, acute polyhydramnios develops between 16 and 24 weeks. Mortality rates are high, reaching 80 to 100% in untreated disorders. There is also high

occurrence of miscarriage, premature rupture of membranes, preterm delivery and spontaneous death of one or both siblings [79].

Quintero’s et al. [80] major classification considers cumulative evolving stages (Table 2). Initial stages only differ in the amount of amniotic fluid in both cavities, followed by signs of anuria in the donor twin (anidramnios or absence of bladder content). An abnormality in the dopplervelocimetry of the donor twin precedes anasarca in the recipient twin. Final stages come with death of one or both fetuses.

I	Maximum vertical pocket <2 cm in donor and >8 cm in recipient sac
II	I + Donor anuria (anidramnios / absence of bladder)
III	I + II + Doppler anomalies in donor
IV	I + II + III + Fetal hydrops
V	I + II + III + IV + Fetal demise

Adapted from Quintero et al, 1999 [80].

**Table 2.** Quintero’s staging of twin-twin transfusion syndrome

This system has some prognostic significance, but the stages not always correlate perfectly with perinatal outcomes. Over 75% of stage I TTTS cases remain stable or regress with conservative management. If treated with suboptimal approaches in non-specialized centers, the consequences can be fatal [75, 77].

### 9.4. Management

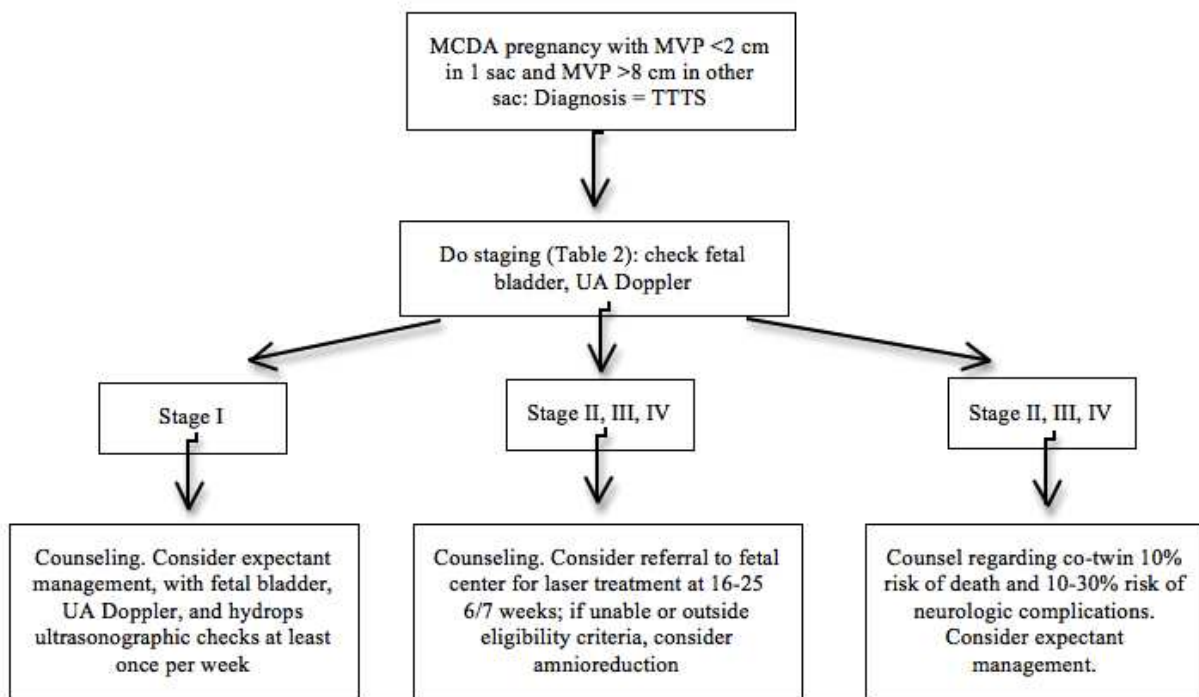
In order to improve the prognosis of TTTS, many options were proposed throughout the years, including specific strategies (selective fetoscopic laser coagulation of placental anastomoses) and non-specific strategies such as expectant management, amnioreduction, septostomy and selective reduction [75, 77]. An algorithm proposed by the Society for Maternal-Fetal Medicine for management of TTTS is shown in Figure 6 [77].

**Selectivefetoscopiclaserphotocoagulation:** first-line treatment for early-onset severe TTTS, requiring highly qualified professionals and specific equipment [75]. Advances in endoscopic surgery allowed proper identification of arteriovenous anastomoses and its coagulation. The rate of survival of at least one fetus is close to 75% and almost 40% of both twins. The overall frequency of neurological impairment is around 4% [81]. This procedure is only performed in severe stages and requires specialized tertiary center, trained staff, and adequate equipment. Maternal morbidity is minimal and complications include miscarriage, preterm premature rupture of membranes, placental abruption, and stillbirth. The Eurofetus trial showed significantly higher survival rate of at least one fetus when comparing laser photocoagulation with amnioreduction (76% vs. 56%) as well as lesser neurological abnormalities (31% vs. 52%) [82].

**Amnioreduction:** progressive polyhydramnios in TTTS increases the risk of preterm premature rupture of membranes and preterm birth, often causing maternal distress. The rationale is to temporarily relieve intrauterine pressure. Serial amnioreduction is usually required, with an average of three procedures until the pregnancy reaches an acceptable gestational age [83]. Complications are similar to fetoscopy, although less frequent and with decreased maternal morbidity. Mean survival rate is 40-50% of at least one fetus and 20% for both. Reported neurological sequels are just about 20 to 30% [84]. The main advantage is that amnioreduction is inexpensive, easy to perform and widely available [74].

**Septostomy:** performed to balance the amniotic fluid amount in both sacs by needle-opening the intertwin membrane. It relieves cameras pressure and may be performed during amnioreduction, with 40 to 83 % survival rate. Septostomy increases the risk of severe complications like cord entanglement and eventual disruption of the membrane. [85]. This procedure has generally been abandoned [75, 77].

**Selectivereduction:** therapeutic option through cord coagulation in order to improve the outcome of the surviving twin whenever there is an imminent risk of spontaneous intrauterine death of one fetus. It can be performed either by ultrasound guided vascular embolization or cord clamping through fetoscopy. A maximum of 50% survival is reached and most services have not supported this technique [86].



MCDA: monochorionic diamniotic; MVP: maximum vertical pocket; UA: umbilical artery

**Figure 6.** Algorithm for management of TTTS. Adapted from American Journal of Obstetrics and Gynecology, Lynn Simpson [77], with permission from the publisher.

### 9.5. Twin Anemia Polycythemia Sequence (TAPS)

Twin anemia polycythemia sequence (TAPS) occurs spontaneously in up to 5% of all monochorionic pregnancies or even after fetoscopic laser photocoagulation, with an estimated prevalence of 13%. This syndrome is characterized by a substantial difference in hemoglobin levels among twins, in absence of discordance in the amniotic fluid. It could be mainly explained by the presence of few persistent arteriovenous anastomoses besides the reduced placental territory where the circulating blood is transferred from donor to the receiver twin, in a unidirectional flow [87].

Prenatal diagnosis may be assessed through the determination of the peak systolic velocity in the middle cerebral artery (PSV-MCA) by dopplervelocimetry. The anemic twin will have a PSV-MCA  $>1.5$  MoM in contrast to a decreased PSV-MCA  $<0.8$  MoM in the polycythemic co-twin [88]. In the postnatal period, diagnostic criteria are based on different levels of hemoglobin between fetuses over 8g/dL, reticulocytes amount over 1.7% or small anastomoses  $<1$ mm [89].

Treatment includes expectant management, labor induction, intrauterine blood transfusion (intravenous or intraperitoneal), selective feticide and fetoscopic laser coagulation. Survival rates up to 80% are achieved when identified in early stages, although there are no studies of long-term neurological outcome [87].

## 10. Selective Intrauterine Growth Restriction (sIUGR)

### 10.1. Causes

Selective intrauterine growth restriction (sIUGR) happens in 10% of monochorionic gestations, similar to dichorionic twins. It is diagnosed when the fetal weight of one twin is under the 10<sup>th</sup> percentile, and frequently there is 25% of discordance. In most cases the origin is in the placental territory discrepancy. Vascular anastomoses between both fetuses intrinsically justify IUGR, and one twin receives better-oxygenated blood [90].

### 10.2. Classification

Although a wide spectrum of vascular anastomoses variations establish different standards for fetal growth, three known patterns of umbilical artery dopplervelocimetry are inclined to develop sIUGR. Type I shows normal diastolic flow in this artery. Constantly absent or reverse flow characterizes type II. Finally, in type III, absent or reverse flow appears intermittently [91].

Prognosis is quite better in type I, contrasting with types II and III, which have been associated to an increased risk of neurological disorders, preterm births and stillbirths. In type III, massive blood transfusion through arterioarterial anastomoses is usually identified [91].

### 10.3. Differential diagnosis between TTTS and early sIUGR

In spite of the available evidence, causes of severe weight discordance in monochorionic pregnancies are still challenging for proper identification. Differential diagnosis demands



early sonographic scanning, along with the exclusion of fetal abnormalities. The development of TTTS is probable once detected any abnormality in the amniotic volume with the larger compartment over 8 cm in one fetus cavity and below 2 cm in the other's. If there is no disturbance of the amniotic fluid and either the estimated weight of one twin is below the 10<sup>th</sup> percentile, or the weight discordance is over 25%, sIUGR may be presumed. Additionally, the evaluation of peak systolic velocity in the middle cerebral artery can be helpful. Finally, if not fitting any of the above criteria, a thorough follow up is recommended [91].

#### 10.4. Management

Type I sIUGR has better prognosis and expectant management is reasonable until 34-35 weeks. Types II and III are associated with worse prognosis, and the therapeutic choice largely depends on the gestational age and severity staging. In these cases, laser therapy and cord occlusion may be practicable alternatives [91].

A fetal medicine specialist must follow monochorionic twins with routine sonographic assessment starting from 16 weeks. Finding any discordance in amniotic fluid or fetal weight, weekly interval is strongly recommended. Except for these cases, monochorionic gestations are expected to undergo an elective resolution around 37 weeks [91].

In our department, types II and III of sIUGR are closely monitored until 26 weeks of gestation, when the patient should be admitted at the hospital for daily Doppler ultrasound scanning, biophysical profile and cardiotocographic exam.

#### 10.5. Twin reversed arterial perfusion sequence (trap sequence)

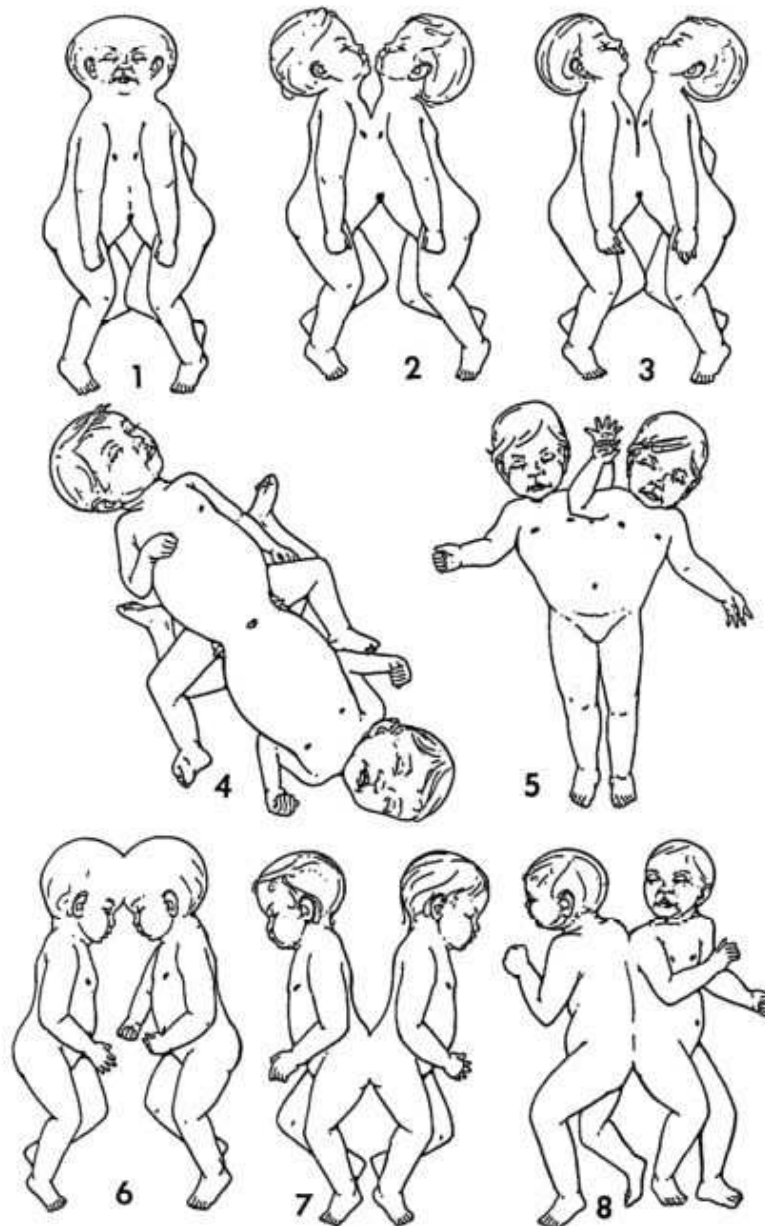
Twin reversed arterial perfusion sequence is a rare malformation in monochorionic pregnancies. The reported incidence is of 1:35000 deliveries and 1:100 monochorionic gestations. Usually, there are multiple structural abnormalities in one of the fetus, varying from a rudimentary heart to its complete absence, and an undeveloped head, associated or not to upper limbs alterations [92].

Generally an edema of the fetal trunk is observed or seen as an amorphous mass. A specific angioarchitecture characterized by an arterioarterial and a venovenous anastomosis supports the development of the acardiac twin. The normal twin acts like an infusion pump, with an increased mortality rate of 50 to 70%. Furthermore, this fetus is threatened by a raised risk of congestive cardiac failure, preterm labor, preterm premature rupture of membranes, premature delivery, polyhydramnios and intrauterine fetal death [75, 93].

Therapeutic options include expectant management, which showed good results when associated to thorough vitality surveillance [94]. There are also invasive procedures to interrupt blood flow to the acardiac twin. Innumerable surgical approaches have been described such as endoscopic cord ligation or compression, bipolar or laser coagulation of the umbilical cord, radiofrequency ablation or even embolization of the vessels inside the abdomen of the acardiac fetus. Despite the success of various techniques, intrafetal ablation is recommended as the best choice concerning its simplicity, safety and effectiveness when compared to others [95].

### 10.6. Conjoined twins and abnormal variations

The union of twins happens once in 50, 000 gestations, and it is related to imperfect segmentation of a single zygote after the 13<sup>th</sup> day of fecundation [96]. A marked female predominance of 72% is registered [97]. Diagnosis is held through early sonography in the first trimester [96]. Attachment may be rostral: omphalopagus, thoracopagus and cephalopagus; caudal: ischiopagus; lateral: parapagus, or dorsal: craniopagus, rachipagus and pygopagus (Figure 7) [98].



**Figure 7.** The eight types of conjoined twins: (1) cephalopagus, (2) thoracopagus, (3) omphalopagus, (4) ischiopagus, (5) parapagus, (6) craniopagus, (7) pygopagus, (8) rachipagus. From *Journal of Pediatric Surgery*, Rowena Spencer [98], with permission from the publisher.

Prognosis is determined according to the site of attachment, organs involved, presence and extension of associated malformations. About 10% of conjoined twins are unequally distributed and 50% have structural anomalies of major organs. Thus, planning for the best correction strategy requires knowledge of cardiac abnormalities, which are frequent in these cases. When a poor outcome is foreseen, vaginal delivery is preferable, although it depends on gestational week and fetuses' dimension [23, 96].

### 10.7. Externally attached parasitic twin

Externally attached parasitic twin is also an infrequent finding in 1:1, 000, 000 births. They are asymmetric conjoined twins in whom a fetus with defect, or a fetal part, is externally attached in a relatively normal twin. Also known as heteropagus twins, it is believed that this type of union results from atrophic ischemia of monozygotic conjoined twins and the parasite twin depends on the cardiovascular system of the other. In most cases the parasite fetus does not have a functional heart or brain [96].



**Figure 8.** Epigastric heteropagus twins. **(A)** Adapted from *Journal of Pediatric Surgery*, *Sharma et al.* [97], with permission from the publisher. **(B)** Adapted from *Journal of Pediatric Surgery*, *Ribeiro et al.* [99], with permission from the publisher.

### 10.8. Fetus In Fetu (FIF)

Fetus in fetu is a seldom finding in monochorionic twins, with incidence of 1:500, 000 deliveries. It has been also detected in adults. Even though already reported elsewhere, the most frequent localization is in the abdominal cavity. It is defined as a fetiform mass incorporated inside a host twin coming from abnormal embryogenesis [100].

FIF happens whenever there is an unequal division of totipotent cells of a blastocyst, resulting in the inclusion of a small cellular mass into a more mature embryo. The main sites of presentation by frequency order are vertebral column, limbs, central nervous system, digestive tract, vessels and genitourinary tract [101]. Karyotype is usually normal and surgery is encouraged to remove the included fetus, not only to relieve its mass effect, but also considering its potential of malignization [100].

### 10.9. Internal teratoma

Internal teratomas are rare congenital tumors, usually benign and of multifactorial etiology. They are constituted by a complex combination of microscopically identifiable tissues inside the fetus, which derivate from mesoderm, endoderm and ectoderm. In its interior, structures like teeth, intestine and hair are covered by connective tissue receiving vascularization from small vessels. It has independent potential of growth and also of malignization [96].

Although prenatal diagnosis can be held by a simple sonographic study within 15-16 weeks, tridimensional evaluation and the use of magnetic resonance may improve diagnostic precision, allowing the establishment of its precise localization, extension, and dissemination.

## 11. Monochorionic twins discordant for fetal defects

The rate of congenital anomalies in twins is 2 times higher than in singletons [102, 103]. In monozygotic twins it is around 5-fold greater. However, in dizygotic twins this rate is similar to singletons. One of the main causes of congenital anomalies in monochorionic twins is related to vascular disruption. The past concept that all monozygotic twins are always identical has changed. The rate of concordant congenital anomalies is 9-18%, even in monozygotic twins [104]. Actually, monozygotic twins are rarely identical once genetic differences exist [105].

There are specific anomalies related to multiple pregnancies, explained by the twinning process and aspects of placentation. The abnormalities of monozygotic twinning include: conjoined twins, TRAP sequence, parasitic twins, and fetus-in-fetu [106]. Monochorionic twin pregnancies have placental vascular anastomoses that could result in TTTS in 15% of cases [107]. Congenital heart defects is 3-fold increased in monochorionic pregnancies with TTTS predominantly affecting the recipient twin, such as ventricular septal defects, pulmonary stenosis and atrial septal defects [108, 109]. The rate of fetal anomaly in monoamniotic pregnancies is around 25%, even if conjoined twins are excluded [106].

A discordant fetal defect in a dizygotic twin pregnancy is easy to explain, since the genetic material is distinct. However, in monozygotic pregnancies, discordant congenital anomalies are related to several mechanisms: missegregation of cytoplasmic material (resulting in different characteristics due to post-zygotic mitotic crossing over or non-disjunction), inactivation or expression of selected genes, imprinting and telomere size differences, X-inactivation and discordant cytoplasmic segregation [110, 111]

Whenever there is a post zygotic non-disjunction in one of the twins, there might be an eventual chromosomal aneuploidy discordance related to chromosomal mosaicism in various degrees. Thus, monozygotic 46, XY and 46, XX twins may be a product of a 46, XXY zygote. Single gene mutation discordances involving either nuclear or mitochondrial DNA as well as X-inactivation and imprinting discordances have occurred. Environmental factors play a major role in epigenetic differences, considering its greatest impact lays on monozygotic twins who were apart the longest [105].

In monochorionic placentas the risk of vascular anastomoses could result in disruption that compromises the fetus. These hemodynamic abnormalities are more prevalent after the death of one co-twin; however, it can happen even in surviving infants. This process of hypoxia and ischemia could affect several organs such as the brain (microcephaly, hydrocephalus or hydranencephaly), the gastrointestinal system (intestinal atresia), the kidney, and the skin (aplasia cutis) [112].

Malformations in twins affect the abdominal wall, skull, and chest, as well as the cardiac, musculoskeletal, urogenital and central nervous systems. They are related to embryonic midline fates (neural tube and cardiac defects), hemodynamic instability of the placenta (brain lesions, limb reduction, cardiac defects, renal agenesis, aplasia cutis and intestinal atresia), and anomalies associated with prematurity (patent ductus arteriosus and retinopathy) [113].

The management of discordant anomalies in monochorionic twins is a great challenge when parents decide to keep the pregnancy. The normal fetus is at increased risk of prematurity and its consequences. The major problem occurs after the death of the discordant fetus for congenital anomalies, which increases the risk of death of the normal co-twin around 10-25%. The risk of brain lesions in the surviving infant is approximately 25% [114]. Also, the rate of perinatal death in twins associated with congenital malformations is approximately 15% [115, 116]. Therefore, it is very important to maintain a strict surveillance during the prenatal in order to diminish the risks for the normal co-twin.

## 12. Fetal death

In general, it is known that multiple pregnancies increase the risk for fetal death. Whenever there is death of one fetus, there is also increased rates of prematurity, neurological sequel and death of the other twin. Chorionicity is determinant in these cases, with more unfavorable prognosis in monochorionic pairs [117].

The vanishing twin syndrome occurs after the sonographic diagnosis of a twin pregnancy, in which a subsequent ultrasound study fails to identify both fetuses. The dead embryo may be completely reabsorbed or even become incorporate into placental membranes, resulting in fetus papyraceous [23, 118].

Later single twin demise in monochorionic twins could also happen due to multiple reasons such as infection, chromosomal or structural anomaly, placental factors or even maternal problems (hypertensive disorder, thrombophilia) [118]. In this scenario, the chance of death of the other fetus and the risk of neurological sequel is around 25% [119]. This can be explained by hemodynamic fluctuations and ischemia, where the blood volume of the living fetus is diverted to the vascular space of the dead fetus, thereby causing multicystic encephalomalacia. Serial ultrasonographic monitoring for brain damage is mandatory and it can be complemented by magnetic resonance imaging. Although the results were inconsistent, some physicians have reported fetal blood sampling and intrauterine transfusion in the surviving twin [118, 120]. Others highlighted the use of ultrasonographic evaluation of the peak systolic velocity in the middle cerebral artery for detection of fetal anemia [121].

It is important to remember the risk of maternal coagulopathy, which although infrequent, is hard to reverse. Even after single fetal demise, the mode of delivery may be vaginal. The exact time of pregnancy's termination depends on a balance between the need to break the unfavorable gradual evolution of the remaining fetus and the establishment of iatrogenic prematurity [118].

### 13. Time and mode of delivery in monochorionic pregnancies

There are many suitable recommendations for twin gestation term in the literature. It is known that the risk of fetal death becomes gradually increased from 38 weeks of pregnancy and it is greater in case of monochorionic pairs [122]. Thus, in many universities' protocols, resolution is recommended for dichorionic pregnancies around 38 weeks, at 37 weeks for monochorionic (devoid of complications) and at 32 to 34 weeks in cases of single amniotic chamber [123].

The main risk associated with vaginal delivery is connected to the possibility of anoxia of the second twin. Thus, studies have shown that elective cesarean delivery at term pregnancy can reduce to 75% the risk of perinatal death [124]. However, a Cochrane systematic review showed that cesarean delivery performed by non-cephalic presentation of the second twin is associated with increased maternal morbidity without improved neonatal outcome [125].

The most important factors in the decision of the delivery mode include the presentation of the fetus, gestational age, and weight or the weight difference between the fetuses. In term births, if only the first twin is in cephalic presentation without detected adversities, vaginal delivery may proceed. If the first twin is neither cephalic, nor presents weight difference for the second fetus, being equal or less than to 500g, caesarean section seems to be a good indication. In preterm pregnancies without other complications or fetal weight lower than 1.500g, a cesarean remains as the best option [126].

Results from the biggest randomized trial conducted by the Twin Birth Study Collaborative Group established major key points [127]. Caesarean section is indicated for all monoamniotic twins, conjoined twins, non-vertex first twin and other classic indications similar to singleton pregnancies. During labour and delivery of a twin pregnancy, neuroaxial anesthesia is preferable. Whenever there is a non-vertex second twin, vaginal delivery is indicated as long as the estimated weight is between 1500-4000g and the obstetrician feels comfortable and skilled [127, 128].

### 14. Conclusion

The frequency of multiple pregnancies has been increasing in the last decades. Currently, it seems to have stabilized mainly due to a more strict regulation of assisted reproductive techniques. Advances in medicine allowed for earlier diagnosis not only of twin pregnancy but also chorionicity and amnionicity characteristics, which are directly implied in adverse

outcomes and prognosis. Despite the various abnormalities related to monochorionic pregnancies, efforts have been made to overcome medical and parenting challenges. Even though twin pregnancies have many peculiarities and must be followed regularly by well-trained professionals, there is no evidence that planned cesarean delivery may diminish fetal morbidity and death.

## Author details

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