

Prematurity and twinning

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Aim of the study: Newborns from multiple pregnancies are increasing in number and demonstrate a higher perinatal morbidity and mortality compared to singletons. Prematurity is the main reason for most neonatal diseases in twins, but other variables may play a role and their prenatal evaluation may improve the overall outcome. **Main findings:** Prematurity is six times more frequent in twins and therefore birth weight is significantly lower compared to singletons. Thus, twins are more exposed to prematurity related diseases (respiratory, cardiovascular, infectious, etc.) and to long-term complications (especially neurological disabilities). **Results:** It is very difficult to estimate the increased risk of neonatal morbidity related to twinning independently to the increased risk of prematurity and therefore to interpret data on morbidity rates, in particular regarding the neurodevelopmental outcome. **Conclusion:** Prevention of preterm birth is a primary goal in managing multiple pregnancies, together with prophylaxis with corticosteroids in order to improve foetal lung maturity. Accurate risk assessment strategies and adequate obstetrical-neonatalogical management of multiple pregnancies may reduce the increasing need for neonatal intensive care and for health resources in the long-term follow-up that has been observed over the last decades.

Keywords: Discordance, growth, morbidity, mortality, outcome, prematurity, twinning

Emerging issues in twins

Newborns from multiple pregnancies are continuously increasing in number and represent about 3% of all newborns, but account for about 15% of perinatal mortality. In fact, they demonstrate a higher risk of morbidity and mortality compared to singletons, which is related to the number of twins, the characteristics of placentation, zygosity, intrauterine growth, gestational age and the eventual use of assisted reproduction technologies (ART) [1,2]. Accurate evaluation of prenatal and perinatal risk factors is mandatory to establish the optimal clinical assessment at birth and the adequate follow-up. Twin newborns, in fact, represent a major concern for neonatal intensive care units (NICUs) and their need for health resources has had an increasing trend over the last decades.

The main clinical issues in twins are prematurity, intrauterine growth restriction (IUGR), malformations and vascular disruptions [3].

Prematurity is six times more frequent in twins and 10 times more frequent in triplets compared to singletons (Figure 1). The mean gestational age is at least 2 weeks lower in twins, 4 weeks

lower in triplets and this gap grows as the number of higher order multiples increases. The birth weight is significantly lower in twins than in singletons, depending on the number of multiples, and this gap appears during the last trimester of gestation, when uterine crowding becomes evident (Figure 2). Specific growth charts for multiple pregnancies and specific inclusion criteria for IUGR are needed to optimize the follow-up procedures for these neonates. All neonatal diseases related to prematurity and low birth weight (respiratory, neurological, infectious, etc.) are more frequent in multiples and require suitable treatment in NICUs [4].

An increased malformation rate at birth have been observed in twin offspring especially for neural tube defects, heart defects, gastro-intestinal and urogenital malformations. Monozygotic (MZ) twins account for most of this higher relative risk, while dizygotic (DZ) twins show a prevalence at birth which is much closer to singletons. Genetic and non-genetic mechanisms may be involved in the genesis of congenital defects, most of which can be considered defects of blastogenesis, and the most evident example of this are conjoined twins. Therefore, the timing of the division of MZ twins after conception plays a key role in determining birth defects [5].

Vascular disruptions are much more frequent in MZ twins and are determined by placental vascular anastomoses. They may be responsible for both foetal and neonatal morbidity and mortality with different clinical presentations depending on the amount, type and timing of anastomosis (foetal loss, foetus amorphous, foetus papiraceus, twin reversed arterial perfusion sequence, twin-twin transfusion sequence, etc.).

The occurrence of any diseases in twins raises the issue of phenotypic concordance or discordance and the subsequent issue of managing pregnancy, patients, parents and decision making events [6]. Risk assessment for the apparently healthy twin, genetic counselling and parental psychological assistance must be part of the clinical follow-up.

In addition, the increasing use of ART with embryo and/or gamete manipulation has been found to determine an increased risk of epigenetic disorders, requiring both adequate preconceptional information and counselling and strict postnatal long-term follow-up.

Prematurity

Preterm birth is defined as a delivery at less than 37 completed weeks' gestation. The increased risk of perinatal morbidity and mortality in twins is mainly related to the increased incidence of preterm birth. In many European countries, about 50% of twins are preterm, accounting for 20–25% of all preterm births. The proportion of preterm births in multiple pregnancies varies widely (for

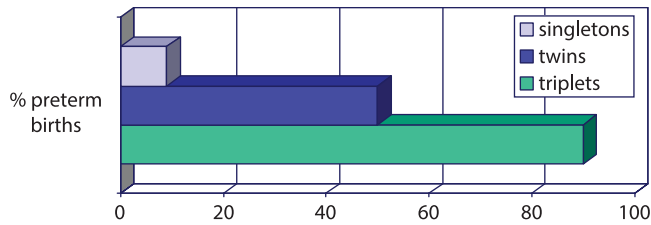


Figure 1. Percentages of preterm births in singletons, twins and triplets.

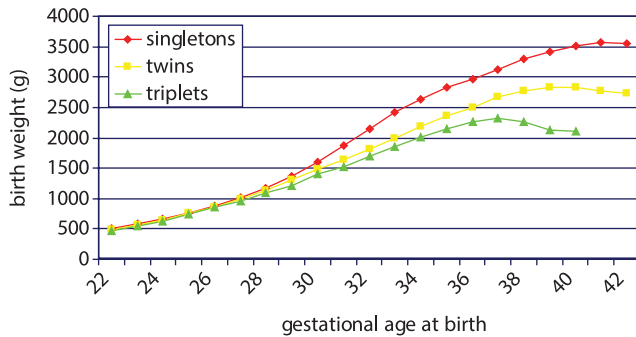


Figure 2. Birth weight per gestational age in singletons, twins and triplets.

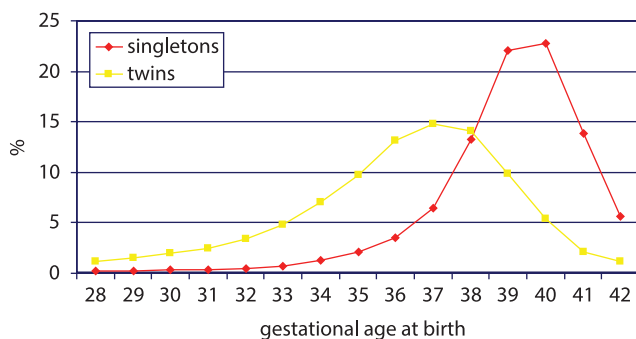


Figure 3. Gestational age at birth in singletons and twins.

example, 68.4% in Austria vs 42.2% in the Republic of Ireland), reflecting different clinical protocols and the consideration of twin pregnancies being high risk and providing social maternal benefits in order to ensure more protection and safety for these pregnancies.

Gestational age at birth tends to decrease from singleton pregnancies to multiple pregnancies as the number of multiples increases [7]. Gestation appears to be at least 2 weeks shorter for twins and 4 weeks shorter for triplets (Figure 3). Many factors play a part in determining this phenomenon: uterine crowding and hyperdistention may often start preterm labour; delivery timing may be anticipated because of medical concern about foetal distress, intrauterine growth restriction (IUGR), twin-to-twin transfusion sequence (TTTS) and twin discordance; the malpractice of programmed elective preterm caesarean section without signs of labour onset still takes place [8]. In addition, multiple pregnancies carry an increased risk of several gestational materno-foetal diseases that may be responsible for preterm delivery themselves: ascending infections because of reduced cervical integrity, psychological and physical maternal stress, cervical incontinence, placental vascular disruptions, hypertension and pre-eclampsia.

Prematurity is directly responsible for the principal neonatal diseases (respiratory, cardiovascular, infectious, etc.) and for

long-term neurological disabilities, therefore, prevention of preterm birth is a primary goal in maternal-infant health care. The high risk of preterm birth should induce clinicians to make a careful assessment of risk factors and to use appropriate diagnostic tests in multiple pregnancies. Intrauterine infections, subclinical chorioamnionitis and other possible direct causes should be excluded. Blood tests and cardiotocographic abnormalities should be accurately considered. Evaluation of cervical length by transvaginal ultrasonography is very useful: cervical length ≤ 25 mm at 18 weeks and ≤ 22 mm at 24 weeks is a good predictor of preterm delivery. Cervical length measurement, together with the fibronectin test and assessment of uterine contractions might diagnose impending preterm birth. Tocolysis and bed rest may delay delivery, in order to permit prophylaxis with corticosteroids to improve foetal lung maturity [9,10]. In cases of severe infection, delivery may well be the best option, combined with antibiotic therapy.

The most evident overall effect of the continually increasing incidence of multiple births is the increased prevalence of premature twins in the NICUs. Prematurity is the main cause of low birth weight, perinatal mortality, and the most frequent determinant of neonatal and infant mortality and morbidity. Its natural consequence is that twins are more exposed to prematurity related diseases and complications: transient tachypnoea of the newborn (TTN), respiratory distress syndrome (RDS), chronic lung disease (CLD) and respiratory failure, patent ductus arteriosus (PDA), persistent pulmonary hypertension (PPN), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH) and brain damage, temperature instability, jaundice and feeding difficulties.

It is, therefore, very difficult to estimate the increased risk of neonatal morbidity and mortality related to twinning independently from the increased risk of prematurity. Many Authors have investigated mortality rates in twins compared to singletons and the higher relative risk for twins appears to be more evident at lower gestational ages (<28 weeks). It is more difficult to interpret data on morbidity rates in twins for specific diseases and, in particular, for late-onset diseases such as neurodevelopmental outcomes [11,12].

Neurodevelopmental outcomes

Developmental research demonstrates that children born very preterm (<32 weeks' gestation) and or with an extremely low-birth weight (ELBW < 1000 g) are at increased risk of neurodevelopmental impairment (NDI), including sensorineural impairments, general cognitive performance, specific cognitive and learning disabilities and emotional and behavioural problems. Most studies on the risks associated with preterm birth look at infants born between 23 and 28 weeks of gestation, but significant brain development takes place in the last four to six weeks of gestation. Recently, several studies have raised concern for modest developmental and academic problems up to age 7 in late preterm babies (born from 34 to 36 weeks gestation). These results indicate that longer-term outcomes of prematurity remain a concern even for those infants born at the more optimistic late-preterm stages of pregnancy. Twins are frequently born preterm or with a low birth weight, so they are at an increased risk of NDI. Major NDI is defined as the presence of at least one of the following: cerebral palsy, developmental quotient (DQ) or intelligence quotient (IQ) <70, deafness, or blindness. Minor NDI is defined as the presence of at least one of the following: mild cerebral palsy causing motor clumsiness or non-fluent gait, DQ or IQ between 70 and 85. Developmental

or mental borderline is defined as DQ or IQ between 70 and 85, and developmental or mental retardation is defined as DQ or IQ < 70 [13]. Epilepsy can be an associated condition. Apart from the described main NDI, several other conditions can be considered to be present in the motor, perceptive, cognitive, emotional and behavioural domains. Major NDI usually becomes evident early in life, while the less severe forms of NDI may become evident several years after birth and be more dependent from the interaction with the environmental context, parenting styles and family dynamics that may differ with multiples compared to singleton.

Twins born at term of gestation have cognitive abilities similar to singletons, but in normal birth weight twins the prevalence of cerebral palsy (CP) is higher [14]. Twinning has been recognized as a risk factor for CP for at least a century [15]. The CP rate per 1000 is 2.3 in singleton survivors, 12.6 in twins and 44.8 in triplets, demonstrating an increased risk in higher order multiple pregnancies [16]. Thus CP is at least five times more frequent among twins than singleton. A recent retrospective cohort study showed that triplets or higher order multiple births are associated with an increased risk of death or NDI at 18–22 months corrected age when compared with ELBW singleton infants and also with twins [17]. However, the real extent of the problem has been underestimated because many infants with severe cerebral impairment that would have presented in the following years as CP do not survive long enough for the diagnosis to be made.

The aetiology of CP, in the majority of cases, is not known but the general consensus is that cerebral impairment occurs during pregnancy. Given that about 1/8 of all natural pregnancies are initially multiple with subsequent spontaneous early loss of one or more foetuses (vanishing twin phenomenon), it has been suggested that a significant proportion of singletons with spastic CP may be the result of the death of a co-twin in the second half of gestation [18]. In monochorionic twin pregnancies, the death of one twin late in gestation is recognized as being an important risk factor for the surviving co-twin to have CP. In MC pregnancies the foetal death of a co-twin increases the risk to as much as 68% (95% CI, 56–78) for preterm delivery of the surviving twin, while in DC this risk is 57% (95% CI, 34–77), and the risk of cerebral palsy (CP) in the surviving twin is 18% (95% CI, 11–26) versus 1% (95% CI, 0–7) in DC pregnancies [19]. The increased risk of CP among twins can be considered a consequence of cerebral injury, which is secondary to haemodynamic disorders during pregnancy or a consequence of postnatal injury associated with prematurity and low birth weight; conditions which are more frequent in twins. In multiple pregnancies, the increased risk of CP is specifically associated with monochorionicity [20]. About 70% of MZ twin pregnancies have MC twin placentas, 98% of which have vascular connections. Twin–twin transfusion syndrome (TTTS), more commonly presenting between 18 and 26 weeks gestation, has an incidence of one in 4000 of all multiple pregnancies (range 0.1–0.9 per 1000), one in 60 of twin pregnancies, and one in five in MZ MC twinning, (range 5–35%) [21]. TTTS is considered the main condition responsible for both a co-twin intrauterine death involving usually the recipient and a serious morbidity involving the surviving donor twin. The survivor can be affected by hypovolaemia due to an acute blood loss through the placental vascular anastomosis into the hypotensive vascular bed of the recipient or dying foetus. Hypovolaemia can, in turn, be responsible for a hypovolemic shock or a severe cerebral hypoperfusion leading to brain ischaemia. The haemodynamic changes observed are not attributable solely to the difference in blood volume between the two foetuses. In fact, the secretion of atrial natriuretic peptide and the suppression of antidiuretic hormone (ADH) in the recipient

twin and changes in gene expression responsible for an increased synthesis of aquaporin (20 times higher) in the donor all play an important role. The renin-angiotensin system is up-regulated in the donor twin and down-regulated in the recipient twin in whom high levels of renin in combination with high levels of endothelin may be jointly responsible for the increased after load. The donor will tend to be anaemic and, due to the contraction of diuresis, will develop oligohydramnios, while the receiver, polycythaemic and hyperbilirubinaemic, will tend to reduce fluid overload by increasing diuresis and thereby will develop a polyhydramnios.

The diagnosis usually relies on ultrasound documenting the simultaneous presence of a foetus with an increased bladder size and polyhydramnios while oligohydramnios will be detected in the co-twin [22]. MR imaging revealed persistently small measurements in the donor cerebrum and cerebellum in comparison with their recipient co-twin and healthy control foetuses [23]. Periventricular white matter lesions (WMLs) and persistent ventriculomegaly in particular have been associated with an adverse neurodevelopmental outcome. WMLs have been detected in one third of monochorionic twin infants at birth, particularly when the pregnancy was complicated by long-term coexistence with a co-twin intrauterine death. Since laser surgery treatment of TTTS was introduced, survival rates have been increasing, and a lower incidence (6%) of cerebral WMLs compared with the cases treated by amnioreduction (18%) has been reported [24]. NDI, however, is still relatively common and not always well documented in long term follow-up studies. Results from some studies report an incidence of major neurological impairment in infancy up to the fourth year of age ranging from 6 to 9%, with an equal incidence of minor neurologic abnormalities in one report [25]. The largest analysis concerning long-term neurodevelopmental outcome after TTTS with laser surgery was published by Lopriore et al. [26]. They investigated 278 children at two years of age (corrected for prematurity). The incidence of major NDI was 18%. They did not report minor NDI. Recently, a study conducted in Japan on twenty survivors of 21 pregnancies with TTTS treated with elective amnioreduction and a mean gestational age at delivery of 28 weeks (range 22–34 weeks), showed a high rate (20%) of major developmental impairment and 10% of minor NDI at a mean age of 6 years (range 3–12 years). Interestingly, children with NDI were delivered before 29 weeks of gestation [27]. Discrepancies among results may be due to differences in diagnostic criteria, disease onset, severity of the TTTS, treatment modalities, and classification of cerebral lesions. TTTS is not considered the unique cause responsible for adverse events in MC preterm twins. MC preterm twins compared to DC twins show ultrasound abnormalities and neurological impairment also in the absence of either TTTS or single intrauterine foetal death. Intrauterine growth restriction (IUGR) occurs in 3–10% of single pregnancies and in 9.1% of twin pregnancies, but with a greater percentage, up to 9.9% in MC twins. In the case of TTTS, twins are frequently discordant with the donor twin often being smaller. Twins are considered discordant in presence of an intertwin difference in birth weight expressed as a percentage of the weight of the heaviest twin $\geq 20\%$. This condition is defined as selective IUGR (sIUGR). In the presence of birth weight discordance, an NDI as detected and the incidence of cranial ultrasound abnormalities consisting in WMLs were higher in MC discordant weight twins (37%) than concordant weight infants (7%). Interestingly, WMLs incidence was also higher in DC discordant compared with concordant weight infants (13 versus 2%; $P < 0.05$), with the incidence of WMLs in MC infants being seven-fold higher than DC infants [28].

A study comparing CP in twins and singletons and examining differences in rates by birth weight but not gestational age showed no significant difference in CP prevalence among lower birth weight groups (<2500 g) whereas the CP prevalence among the larger (≥ 2500 g) twins compared to singletons is highly significant. A study aimed at evaluating the excess risk of CP for twins compared with singletons, which is not explained by low birth weight or prematurity, a well-known risk factor for CP both affecting singletons and twins, affirmed that the CP rates for twins vary less with birthweight and gestational age than the rates for singletons. The observed differences between twins and singletons in the CP prevalence that is four to five times higher in twins cannot simply be attributed to lower birth weight and prematurity. Monochorionicity and sIUGR can be considered the main risk factor responsible for the higher CP prevalence risk in twins.

Cerebral palsy is classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed.

A study showed that almost 65% of twins were affected by spastic bilateral CP compared with less than 50% of singletons [29]. Different types of CP are more frequent depending on the specific class of twins. Specifically, the risk of spastic bilateral CP is higher for low birth weight infants than the risk of spastic hemiplegia which is more likely to be found in infants weighing over 2500 g. In the singleton population, only about 5% of the infants weighed less than 2500 g at birth. This compares with over 50% for the twin population, while for the twins with CP, 84% had birth weights below 2500 g.

MC and twin birth weight discordance are the only variables associated to a higher prevalence of language delay, cognitive and attention deficit at the age of 4 years [30]. MC twins, especially if born prematurely and sIUGR, are at a higher risk not only of major neurological sequelae such as CP and neurosensory deficits, but also of minor neurodevelopmental sequelae, potentially leading to future academic and social integration difficulties. Thus, infants from multiple pregnancies should receive a careful developmental surveillance with parents' full cooperation and an individualized neurodevelopmental follow-up with appropriate multidisciplinary support.

Twin discordance and ethical issues

Twin discordance for the presence of a pathological condition, especially if lethal or invalidating, raises serious concern in terms of the bioethical and psychological impact on the parents and medical staff. Different choices can be considered in managing these multiple pregnancies: termination of pregnancy, selective embryo reduction of the affected twin, anticipation of delivery or natural course of the pregnancy. Each choice hides difficult clinical and legal implications because it may directly or indirectly involve and compromise the healthy twin as well as the mother [31].

Accurate clinical, laboratory and ultrasonographic evaluation together with pregnancy follow-up are essential for reaching the correct diagnosis and consider prognosis and therapeutic options (prenatal and postnatal) as a result. The risk of intrauterine death and potential risks for the other twin and the mother must be taken into account. Sometimes it is possible to wait until the natural end of pregnancy and then provide suitable treatment to the affected twin. Other times, parents opt to terminate the pregnancy, thus losing both twins (healthy and affected). A selective reduction (after accurate evaluation of placentation) of the affected twin may allow the pregnancy to be continued for the healthy infant, but it carries a high risk of complication for the other twin, especially in monochorionic pregnancies [32]. In many cases observed in the

late third trimester of pregnancy, the option of a preterm delivery can be considered and may contribute to the increase of prematurity and prematurity related diseases in twin offspring.

The management of multiple pregnancies appears to be a complex task for medical staff and requires a multidisciplinary team to support parents with adequate counselling and psychological help.

Declaration of Interest: The authors report no conflicts of interest.

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