**Abstract**

**Aim:** In the current review study, we present recent data regarding the importance of intertwin estimated fetal weight (EFW) and crown rump length (CRL) discordance for the prediction of adverse perinatal outcome both in monochorionic and in dichorionic diamniotic gestations.

**Results:** Twins with significant weight disparity are associated with higher rates of perinatal morbidity and mortality, regardless of gestational age at delivery. However, there is no agreement regarding as to the cut off value above which the perinatal outcome is unfavorably affected and the threshold range from 10 to 30%. On the other hand, CRL discrepancy has proved to be a weak predictor of adverse outcomes, such as fetal or neonatal death in fetuses without chromosomal and structural abnormalities. In clinical practice, decisions about obstetric surveillance of discordant twin gestations, frequency of fetal sonographic monitoring and time of delivery are usually based on amniotic fluid volume and Doppler assessments on a weekly basis.

**Conclusion:** Significant EFW discordance leads to adverse perinatal outcome, although the cut-off value has not yet been estimated. CRL discrepancy is not correlated well with adverse perinatal outcome. However, increased monitoring of women with EFW and CRL discrepancy is suggested.

**Keywords:** Adverse perinatal outcome; crown-rump length; dichorionic pregnancy; estimated fetal weight discordance.

**Introduction**

During the past few decades there has been a significant increase in the proportion of multifetal gestations. One fourth to one third of them is due to an increase in maternal age. The performance of assisted reproductive techniques and the induction of multiple ovulation are responsible for 30–50% of the twin pregnancies and at least 75% of the triplets [1].

Although multifetal pregnancies represent a minority of births, they account for a disproportionate share of perinatal morbidity and mortality. Many studies have been conducted in order to identify factors affecting the perinatal outcome of such neonates.

Fetal growth in multiple gestations follows different patterns compared to singleton pregnancies [2]. Twins are usually smaller than singletons as a result of normal adaptation mechanisms. The uterus is characterized by a unique capability of enlarging up to a certain degree. As the uterus reaches its limitations in volume and nutritional capacity, fetal growth is reduced in one or both fetuses. Therefore, an intertwin growth disparity within certain limits is a normal condition in some twins [2].

Growth discrepancy is expected to a certain extent both in monochorionic and in dichorionic gestations and may constitute a physiological adaptation. However, monochorionic twin pregnancies are complicated by such discordances twice as often as dichorionic ones. Higher degrees of growth discordance are accompanied by higher rates of perinatal mortality and morbidity both in the smaller and in the larger twin [3–5]. The current review serves to explore the importance of inter-twin estimated fetal weight (EFW) and crown rump length (CRL) discordance for the prediction of adverse perinatal outcome.
Incidence of discordant twin growth

A discrepancy in growth and birth weight is frequently recorded within twin pairs. Specifically, in 18% of twins, birth weight differs from 500 g to 999 g and the difference is >1000 g in 3% [6]. A birth weight discrepancy of approximately 20% exists in 15–30% of twins. Furthermore, a discordance of 20% between the largest and the smallest neonate appears in more than 40% of triplet gestations, with 7% exceeding 40% discrepancy [6].

Etiology

Many extensively investigated factors have been causally associated with the growth discordance and the subsequent birth weight disparity between neonates of dichorionic diamniotic pregnancies. These factors can be briefly separated into two categories: (a) constitutive genetic factors (differences in growth potential-genetic heterogeneity of twins) and (b) uteroplacental factors, such as infarcts and hematomas of the placenta, a non-central placental cord insertion or single umbilical arteries.

On the contrary, growth discrepancy in monochorionic gestations is attributable to unequal placental sharing and vascular anastomoses [7]. As far as the inadequate placental partition is concerned, not only has it been etiologically correlated with weight discrepancies, but it has also been considered as the most important determinant of growth discrepancies.

Besides the uneven placental territory, growth in monochorionic twins is influenced by the presence of intertwin vascular connections [8]. Three types of anastomoses can be found in monochorionic placentas: arterioarterial (AA), venovenous (VV) and arteriovenous (AV). While the first two types allow bidirectional blood flow through connections on the surface of the placenta, the arteriovenous anastomoses may lead to unidirectional flow through deep capillary beds within the cotyledons and cause volume imbalance between the twins [8].

In a large, multicenter, prospective study (ESPRiT) [9] of twin pregnancies, the association between placental histological abnormalities, birthweight discordance and growth restriction was examined. This study indicated a correlation between placental abnormalities with birth weight discrepancy and intrauterine growth restriction in dichorionic twins. On the other hand, no such association was observed in monochorionic twin pregnancies [9].

Unique aspects of monochorionic twins

The existence of some unique complications in monochorionic twin gestations, such as the twin-to-twin transfusion syndrome (TTTS), the twin anemia polycythemia sequence (TAPS), the twin reversed arterial perfusion (TRAP) sequence, is mainly due to the vascular anastomoses and to the subsequent intertwin blood exchange [8]. Twin-to-twin transfusion syndrome, which affects about 10–15% of all monochorionic twins, is diagnosed in the case of amniotic fluid discordance in monochorionic pregnancies and especially in the presence of oligohydramnios [a maximal vertical pocket (MVP) of <2 cm] in the donor sac and polyhydramnios (MVP >8 cm) in the recipient sac [10]. Apart from the amniotic fluid discrepancy, signs of cardiac disfunction in the recipient twin such as cardiomegaly and myocardial hypertrophy may contribute to the differential diagnosis between growth restriction and twin-to-twin transfusion syndrome [11].

A classification system based on the umbilical artery (UA) Doppler waveforms of the smaller twin has been proposed for monochorionic twins with growth discordance. According to Gratacós et al. [12] fetuses are classified as Type I in the case of positive end-diastolic flow, Type II in the case of persistent absent or reversed end-diastolic flow (AREDF) and Type III in the case of intermittent absent or reversed end-diastolic flow (iAREDF). Both the prognosis and the optimal management differ in each subgroup. Whereas Type I cases are associated with low rates of neurological damage and fetal demise, Types II and III cases are at high risk of adverse outcomes such as very preterm delivery, parenchymal brain damage of the larger twin and intrauterine fetal death of the smaller twin [7, 12].

Estimated fetal weight discordance and perinatal outcome

One of the crucial dilemmas posed is whether discrepant twin growth is an independent risk factor for subsequent adverse perinatal outcomes, or it is just an ultrasound observation which may be associated with high rates of perinatal morbidity and mortality. Another important question is the threshold for significant growth discordance. Otherwise, both the discordant twin and the normally grown twin will be considered as being at increased risk of obstetric interventions such as, iatrogenetic preterm birth and subsequent prematurity.
Discordant twin growth has been associated with an increase in the perinatal morbidity and mortality, as well as, physical and neurodevelopment complications on a long-term basis. Some studies have identified discrepant twin growth as an independent risk factor for poor perinatal outcomes [13–15], whereas others relate the higher rates of perinatal morbidity and mortality in twin pregnancies with co-existing factors, such as gender discordance, actual birth weight, gestational age at delivery, twin-to-twin transfusion syndrome in monochorionic twins, or selective fetal growth restriction [16–18]. Growth discrepancy among co-twins of a dizygotic pair may be a result of constitutional genetic differences and up to the level of 10% is considered to be normal [19].

There is as yet no consensus regarding the cut-off value above which third trimester inter-twin weight discrepancy leads to adverse perinatal outcome. In retrospective studies the threshold range from 10 to 30% [4, 5, 9, 19–24] (Table 1). According to the American College of Obstetricians and Gynecologists [27] an EFW disparity of approximately 15–25% is considered to be clinically significant, whereas the UK National Institute for Health and Care Excellence guidelines [28] set the threshold at the level of 25% and recommend the referral of such pregnancies to a tertiary fetal medicine center.

In a large, multicenter, prospective study (ESPRiT) [3] the cut-off value of the EFW discordance above which, the risk for poor perinatal outcomes becomes 2-fold more than the risk in singleton pregnancies, stands at 18% for both dichorionic twins and monochorionic twins without cases of twin-to-twin transfusion syndrome. However, the same study reaches the conclusion that discordant monochorionic twins face higher absolute morbidity risks in comparison with discordant dichorionic twins at all stages of birth weight discordance [3]. A large retrospective study (STORK) [26] of 2161 twin gestations revealed that a discrepancy in EFW >25% is the threshold for the prediction of perinatal loss and is associated with an increased risk of neonatal mortality. According to the authors, a threshold of 25% exists regardless of chorionicity or fetal weight. Such pregnancies require increased obstetric surveillance from 26 weeks of gestation, whereas the optimal time of delivery seems to be the 38th week of gestation [26].

It is obvious that, even among recent extensive studies, there is a lack of agreement on the cut-off value above which the perinatal outcome is adversely affected. The ESPRiT study sets a threshold level of 18% for dichorionic twin gestations, while the STORK study sets a threshold level of 25% irrespective of chorionicity. Differences in the design of the two studies could have contributed to this. The ESPRiT study is a prospective study of 1028 dichorionic twin pregnancies, wherein the fetal weight was estimated in the 24th week of gestation. On the other hand, the STORK study is a retrospective study of 2161 twin pregnancies regardless of chorionicity, wherein the fetal weight was estimated at the 26th week of gestation.

Khalil et al. [24] have recently performed fetal biometry as well as fetal Doppler assessments in order to evaluate their accuracy in predicting perinatal mortality in twin gestations. The authors concluded that a combination of discordances in the EFW and the cerebroplacental ratio (CPR) (defined as the ratio of middle cerebral artery pulsatility index-MCA PI to umbilical artery pulsatility index-UA PI) can detect most of twin pregnancies facing the risk of perinatal loss. On the contrary, D’Antonio and co-workers [25] demonstrated that second trimester EFW disparity is a poor predictor of adverse perinatal outcomes such as perinatal loss and fetal loss after 22 or 28 weeks of gestation both in monochorionic and dichorionic twin pregnancies.

Other studies have examined the possible use of abdominal circumference (AC) instead of EFW in order to predict adverse perinatal outcome. According to Hill and co-workers [29] an inter-twin abdominal circumference (AC) disparity of 20 mm or more had a sensitivity of 83% to detect a twin birth weight discordance of approximately 20%. On the contrary, EFW had a sensitivity of 92%, while at the same time the positive predictive value reached the level of 72% [29]. The authors [29] concluded that EFW

Table 1: Studies published during last decade including data on clinical significance of intertwin weight discordance.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases (n) [twin-pairs]</th>
<th>Study design</th>
<th>Chorionicity</th>
<th>Weight discordance cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khalil et al. [24]</td>
<td>620</td>
<td>Retrospective</td>
<td>MC and DC</td>
<td>26.5%</td>
</tr>
<tr>
<td>D’ Antonio et al. [25]</td>
<td>2399</td>
<td>Retrospective</td>
<td>MC and DC</td>
<td>Not identified</td>
</tr>
<tr>
<td>Mottet et al. [22]</td>
<td>67</td>
<td>Retrospective</td>
<td>DC</td>
<td>&gt;30% (“severe”)</td>
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<tr>
<td></td>
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<td></td>
<td>25–30% (“moderate”)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>20–25% (“slight”)</td>
</tr>
<tr>
<td>D’ Antonio et al. [26]</td>
<td>2161</td>
<td>Retrospective</td>
<td>MC and DC</td>
<td>25%</td>
</tr>
<tr>
<td>Breathnach et al. [3]</td>
<td>1028</td>
<td>Prospective</td>
<td>MC and DC</td>
<td>18%</td>
</tr>
<tr>
<td>Kato et al. [20]</td>
<td>56,033</td>
<td>Retrospective</td>
<td>No analysis by chorionicity</td>
<td>15%</td>
</tr>
</tbody>
</table>
was a more sensitive marker than AC in predicting twin weight discrepancies, but with a significantly lower positive predictive value.

Estimating the threshold of twin EFW discordance which is associating with adverse perinatal outcome, it is important to emphasize that it is hampered by cases of intra-uterine growth restriction (IUGR) and small for gestational age (SGA) fetuses. Weight discordance and IUGR are all facets of the same entity. When birth-weight disparity rises up to 20%, there is more than a 50% possibility that one of the fetuses will be IUGR [19]. In cases of a SGA fetus (below the 5th percentile), the intertwin EFW discordance threshold of 18% quadruples the risk of adverse perinatal outcome for the SGA fetus [3]. Furthermore, growth discordant twins face an increased risk of adverse perinatal outcome (2-fold risk) even in cases where the birth weight is within normal range [3].

Crown-rump length discordance and perinatal outcome

Given the constraints on EFW in twins, attention has been drawn to other predictive markers of poor perinatal outcome and especially to the crown-rump length (CRL) in the first trimester of pregnancy. Kalish et al. [30] demonstrated that, twins with birth weight discordance may differ in fetal size as early as at 11–14 weeks of gestation. Furthermore, fetuses with identical CRL measurements are significantly less likely to develop a subsequent growth discrepancy [30]. Despite the fact that CRL measurements are not considered to be an ideal screening test for birth weight discordance, they can be used to identify patients at increased risk for poor perinatal outcome. An intertwin CRL difference greater than the 90th percentile in the first trimester is associated with increased risk of birth weight disparity and intrauterine growth restriction [30].

Several retrospective studies demonstrated that an intertwin CRL disparity identified early in the first trimester might predict several adverse perinatal outcomes or even fetal loss [31–33]. However, some of the studies excluded monochorionic gestations, whereas the majority of them included a relatively limited number of patients. As a consequence, their strength was restricted. The STORK study [34] was designed in order to evaluate the correlation between discordance in intertwin embryonic growth at 7–9+6 weeks of gestation and single embryonic loss at 11–14 weeks of gestation. The cohort included twin pregnancies with known chorionicity (288 monochorionic and 1068 dichorionic) presenting early in the first trimester while a systematic review of the literature was performed at the same time. According to the STORK study, an intertwin CRL disparity detected at 7–10 weeks represents an independent risk factor for fetal loss at 11–14 weeks [34]. When this difference reaches 19%, sensitivity and specificity rise to 87.4 and 95.2%, respectively. Furthermore, the greater the CRL discrepancy is, the greater the likelihood of early fetal loss at 11–14 weeks of gestation is [34]. On the contrary, neither maternal age nor chorionicity were identified as risk factors for single fetal loss at 11–14 weeks [34].

Harper et al. [35] performed a cohort study based on similar principles (retrospective study, first-trimester ultrasound between 7+0 and 14+0 weeks of gestation). The primary outcome was the loss of one or both fetuses before 20 weeks of gestation in a population of 805 dichorionic twin pregnancies. The study revealed an increased possibility of structural fetal abnormalities or fetal loss before 20 weeks of gestation in case of CRL discordance of at least 11% [35]. The authors emphasized, however, that no other adverse outcomes such as growth restriction or preterm birth have been demonstrated in surviving pregnancies of anatomically normal fetuses beyond 20 weeks of gestation [35].

A series of previous studies have indicated a correlation between intertwin CRL discrepancy in first trimester and poor perinatal outcome (intrauterine death, perinatal mortality, preterm birth) [30, 35–48] (Table 2). Nevertheless, most of them failed to verify the predictive value of CRL discrepancy for adverse outcome. In addition, several of these studies included gestations with structural malformations as well as cases of chromosomal abnormalities [35–39]. In order to avoid these limitations, D’Antonio et al. [50] excluded such pregnancies from a recent retrospective study of 2155 twin gestations (420 monochorionic and 1735 dichorionic). It was substantiated that in the absence of aneuploidy or structural fetal abnormalities and regardless of chorionicity, CRL discrepancy is not a crucial predictive factor for adverse outcomes such as neonatal morbidity, preterm birth, IUGR and intertwin EFW difference of more than 25% [50]. Considering these data, D’Antonio et al. do not recommend the establishment of intertwin CRL discordance as a routine screening test [50].

Another recent retrospective study of 1993 twin pregnancies (1733 dichorionic and monochorionic) by Johansen et al. [49] assessed similar outcomes. An intertwin CRL disparity of more than 10% was identified as an extremely weak predictive marker of intrauterine death, whereas it was revealed to be poorly associated with preterm birth, as well as birth weight discrepancy, in dichorionic twin gestations [49]. Finally, Fratelli et al. [47] failed to substantiate a correlation between the difference in nuchal translucency (NT) and CRL and development
of twin-to-twin transfusion syndrome in monochorionic twin pregnancies.

Clinical management

Clinical management of monochorionic and dichorionic twin gestations with CRL or EFW discrepancy is a challenge for any obstetrician. In general terms, management should be focused on three major points: the level of obstetric surveillance, the antenatal corticosteroid therapy and the decision about timing of obstetric intervention-delivery. Most of the recently published data agree on a fetal sono-graphic monitoring of such pregnancies on a weekly basis, which should include the assessment of the volume of amniotic fluid and a multivessel Doppler evaluation of the fetuses. Estimation of the fetal growth should be performed every 2–3 weeks. When crucially abnormal umbilical artery (absent or reversed end diastolic flow) or venous Doppler waveforms beyond the 28th week of gestation are noticed and the estimated fetal weight is sufficient, then delivery is probably the optimal management [19].

As far as Type I discordant monochorionic twins are concerned, they should be managed expectantly with Doppler assessments every 7–14 days until the 34th–35th week of gestation [5, 8]. On the contrary, there is no consensus as to the optimal management of Type II and III twins, which varies from elective fetal therapy to close surveillance and elective delivery and depends among others on gestational age, parents’ wishes and the degree of fetal deterioration [7, 10].

Conclusion

The intertwin growth disparity should be regarded as a unique pathological entity, presumably caused by local placental implantation factors or genetic differences in dichorionic twins and by vascular anastomoses or unequal placental territory in monochorionic gestations. There is as yet no consensus about the cut-off value above which the perinatal outcome is adversely affected, especially considering the SGA fetuses. Recent studies demonstrate that, an intertwin EFW discordance of more than 25% is associated with an increased risk of perinatal mortality, irrespective of chorionicity and actual fetal weight. Such cases require heightened fetal scrutiny, comprising of evaluation of the volume of amniotic fluid and a multivessel Doppler assessment. As far as CRL discrepancy is concerned, the majority of the recently published data do not indicate a significant correlation between intertwin CRL discordance and prediction of adverse perinatal outcome.

References


The authors stated that there are no conflicts of interest regarding the publication of this article.