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Prediction of outcome in twin pregnancy with first and early second trimester ultrasound

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Abstract

Objective: To establish if first or second trimester biometry is a useful adjunct in the prediction of adverse perinatal outcome in twin pregnancy.
Methods: A consecutive cohort of 1028 twin pregnancies was enrolled for the Evaluation of Sonographic Predictors of Restricted growth in Twins (ESPRiT) study, a prospective study conducted at eight academic centers. Outcome data was recorded for 1001 twin pairs that completed the study. Ultrasound biometry was available for 960 pregnancies. Biometric data obtained between 11 and 22 weeks were evaluated as predictors of a composite of adverse perinatal outcome (mortality, hypoxic ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress, or sepsis), preterm delivery (PTD) and birthweight discordance greater than 18% (18% BW). Outcomes were adjusted for chorionicity and gestational age using Cox Proportional Hazards regression.
Results: Differences in crown-rump length (CRL) were not predictive of adverse perinatal outcome. Between 14 and 22 weeks, a difference in abdominal circumference (AC) of more than 10% was the most useful predictor of adverse outcome, PTD and 18% or more BW discordance in all twins. Overall the strongest correlation was observed for intertwin differences in biometry between 18 and 22 weeks.
Conclusion: Biometry in the early second trimester can successfully identify twin pregnancies at increased risk. Intertwin AC difference of greater than 10% between 14 and 22 weeks gestation was the best individual predictor of perinatal risk in all twins. Sonographic biometry in the early second trimester should therefore be utilized to establish perinatal risk, thus allowing prenatal care to be improved.

Keywords

Pregnancy, pregnancy outcome, twins, ultrasound

History

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Introduction

The twin birth rate has climbed by approximately 50% in the United States over the past 20 years. Similarly, in the UK the twin birth rate has risen from 10.1 per 1000 in 1985 to 15.5 per 1000 in 2010. This rise is due in part due to improved assisted reproduction, creating a unique set of challenges for the obstetrician [1].

Growth discordance in excess of 20% between co-twins occurs in approximately 16% of twins [2]. It is well established that growth discordance in twins in the third trimester is associated with a variety of complications and adverse perinatal outcome [3], therefore the early identification of twins at risk of discordance at an early stage would be beneficial in many ways. It has not been previously well established, how early this intertwin discordance becomes apparent and what degree of discordance is significant. Both CRL differences in the first trimester [4], and AC differences later in pregnancy have been shown to be of use as predictors of discordant growth [5].

Previously it has been demonstrated that birthweight discordance-related risk of fetal and neonatal mortality is higher in smaller twins than larger twins. Perinatal mortality is also higher in term twins than preterm twins and in small twins that are also small for gestational age [6,7]. In addition, discordance of more than 20% was found to be predictive of an increased rate of preterm birth, late miscarriage, polyhydramnios, placental abruption and fetal malformation [8].

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Our group has recently shown that a birthweight difference of 18% or more in both monochorionic and dichorionic twin pregnancy is associated with increased rates of perinatal mortality and morbidity (including respiratory distress syndrome, hypoxic-ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis or sepsis) even if the weights are both within the normal range [9]. Our group has also recently shown that monochorionic twin pregnancy is associated with a 1.5% late *in utero* death rate, highlighting the need for identifying those at increased risk [10].

The objective of this study was to determine the ultrasound biometric parameters in the first and early second trimester that can predict adverse pregnancy outcome. The ability to identify a group of twin pregnancies at higher risk of adverse outcome would allow for targeted antenatal surveillance with the potential to improve perinatal outcome.

Methods

A consecutive cohort of 1028 unselected twin pregnancies was enrolled for the ESPRiT study (Evaluation of Sonographic Predictors of Restricted growth in Twins); a multicenter prospective study conducted at eight academic perinatal centers in Ireland, all with tertiary neonatal intensive care facilities, from March 2007 to June 2009 [11,12]. Institutional Review Board approval was obtained at each participating site and the study participants gave written informed consent. For this pre-specified secondary analysis, inclusion criteria were all twin pregnancies presenting to the study centers between 11 and 22 completed weeks' gestation, with both fetuses alive at the time of prelabor Cesarean delivery or of onset of labour. Monoamnionicity, a major structural abnormality in either twin, or fetal aneuploidy led to exclusion from the analysis.

For patients meeting inclusion criteria, ultrasound examination comprised biometric parameters, placental location, cord insertion site and determination of chorionicity at enrolment (mean 16 (range 13–19 weeks) and again at 18–20 weeks for those enrolled prior to 18 weeks. All scans were carried out using GE Voluson Expert 730® equipment (General Electric Company (GE), Fairfield, CT, USA).

In the first trimester CRL was recorded for each fetus and from 14 weeks gestation BPD, HC, AC and FL measured. First trimester scans were not recorded on all women as many attended for their first visit after 12 weeks gestation. Nuchal translucency was not routinely measured. This was recorded in those who requested first trimester screening for aneuploidy. Two-weekly growth scans were performed for all twin pregnancies from 24 weeks' gestation until delivery and umbilical artery Doppler and middle cerebral artery Doppler were measured in addition to routine biometric parameters. For monochorionic twins, two-weekly ultrasound surveillance was initiated at 16 weeks' gestation. A quality review system was in place, requiring regular submission by sonographers of images and Doppler traces to a central ultrasound quality assurance committee.

All obstetric and ultrasound data were contemporaneously transferred to an ultrasound software system (Viewpoint®, General Electric Company (GE), Fairfield, CT, USA) and uploaded onto a live web-based central consolidated database. Pediatric outcomes for all twins not requiring neonatal intensive care were recorded by the research sonographer and uploaded onto the consolidated database. Infants requiring neonatal intensive care had their outcomes recorded by pediatric staff.

Management decisions relating to timing and mode of delivery were at the discretion of the lead clinician managing each twin case. Across all eight centers the intrapartum management protocol for twin birth included the routine use of regional anesthesia, continuous intrapartum fetal heart rate monitoring, immediate access to the operating suite for emergency Caesarean delivery, and all obstetricians in this system were skilled in operative vaginal delivery, breech extraction and internal podalic version. Tertiary-level neonatal care facilities were available in all eight sites.

Neonatal intensive care unit or special care baby unit admission was used as an indicator for neonatal morbidity and length of neonatal inpatient stay was recorded. In addition, a composite measure of adverse perinatal outcome was analyzed according to mode of delivery. This measure included either perinatal mortality or any of the following: hypoxic ischemic encephalopathy (HIE), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), respiratory distress or sepsis. A diagnosis of hypoxic ischemic encephalopathy was recorded in the setting of profound umbilical arterial acidemia ($pH < 7$), persistence of an Apgar score of 3 or less for longer than 5 min, neonatal neurologic sequelae and multiple organ involvement. Periventricular leukomalacia was diagnosed by neonatal ultrasound and subsequent magnetic resonance imaging. A diagnosis of respiratory distress was made for any infant requiring respiratory support and supported by radiographic criteria. Length of oxygen-dependence was also recorded. A diagnosis of neonatal sepsis was made on the basis of clinical signs together with positive microbiological cultures.

Ultrasound biometric parameters including crown rump length, biparietal diameter, head circumference, femur length, abdominal circumference (AC) and estimated fetal weight were analyzed. Their predictive value for a composite of adverse perinatal outcomes, perinatal mortality, preterm labor and clinically-significant growth discordance was established.

Statistical analysis

Perinatal outcomes were modeled according to gestational age of delivery using Cox Proportional Hazards for each biometric parameter. Monochorionic and dichorionic twins were analyzed separately in addition to the cohort as a whole. Biometric parameters were dichotomized to 10% and 20% intra-twin differences for the ease of description. The analyses were adjusted for covariates maternal age, maternal BMI, cord insertion site (central/non-cental), assisted reproductive technology (yes/no) and chorioncity in the whole cohort analysis. The composite outcome consisted of any mortality, IVH, HIE, PVL, NEC, RDS or sepsis in either twin. Preterm delivery (PTD) was defined as delivery prior to 34 completed weeks' gestational age.

To account for the multiple testing of different outcomes for each of the biometric parameters for each gestational age range, all statistical analyses were adjusted using the Bonferroni Correction thereby minimizing the possibility of presenting false-positive conclusions.

Results

Totally 1001 twin pregnancies recruited during the two-year study period (May 2007 to October 2009) completed the prenatal fetal surveillance schedule and delivered at one of the eight participating perinatal centers. An additional 27 recruited patients did not complete the study due to transfer of obstetric care to a non-participating center, withdrawal from the study or loss to follow-up. Pre-viability single or dual fetal demise was identified in 24 pairs, such that perinatal outcome data was recorded on 100% (977/977) of participants who had two live fetuses with intact membranes at 24 weeks' gestation, without the presence of major structural or chromosomal abnormality. Within this cohort, 14 pregnancies were complicated by twin–twin transfusion syndrome.

Ultrasound biometry was available for 960 pregnancies between 11 and 22 weeks. Of note more data was available as gestational age increased with 265 (27.6%) available at gestational age 12–14 weeks, 441(45.9%) at 14–18 weeks and 871(90.7%) at 18–22 weeks (Table 1). Maternal characteristics of this cohort have been previously described (Breathnach et al 2011). In summary the mean maternal age was 32.7 years, (range 14–37), 52% were multiparous, 27% had assisted conception, mean gestational age at delivery was 36 weeks, (SD = 2.6), mean birthweight was 2.46 kg, (SD = 0.6), 65.3% were delivered by caesarean section and 49% required admission to the neonatal intensive care unit. Table 1 shows that the maternal characteristics, used as covariates in the statistical models, were similar across the gestational age categories. The primary findings for the whole cohort are presented in Tables 2 (CRL and AC) and Table 3 (FL, EFW and BPD). Note that any statistically non-significant findings may have been attributable to small sample size, small effect size, large variation or a combination of these factors.

Differences in CRL of 10% or 20% were neither predictive of adverse perinatal outcome in all twins taken as a group, nor in DC or MC twins. Of note inter-twin differences in CRL among monochorionic twins did not predict later development of TTTS.

Between 14 and 22 weeks gestation inter-twin differences in BPD, HC, FL, EFW showed elevated risks of adverse perinatal outcome. However, these were not statistically significant after adjustment for multiple comparisons. Between 14 and 18 weeks gestation >10% inter-twin difference in AC showed an increased risk for birthweight discordance of 18% or greater,

Table 1. Ultrasound biometry and adverse perinatal outcome.

	Gestational Age*			
Maternal Characteristic/Outcome	11 + 0 to 21 + 6 weeks (*N* = 960)	11 + 0 to 14 + 0 weeks (*N* = 265)	14 + 1 to 17 + 6 weeks (*N* = 441)	18 + 0 to 21 + 6 weeks (*N* = 871)
Maternal age (mean years)	32.7	32.5	32.8	32.8
BMI (mean)	25.4	24.9	25.1	25.3
Cord Insertion Site				
• Central/central	503 (68%)	138 (63%)	208 (62%)	457 (68%)
• Central/non-central	173 (23%)	61 (28%)	88 (26%)	159 (24%)
• Non-central/non-central	63 (9%)	19 (9%)	37 (11%)	59 (9%)
ART	227 (27%)	70 (30%)	117 (31%)	212 (28%)
Composite adverse perinatal outcome	203 (21%)	36 (14%)	97 (22%)	194 (22%)
18% BW discordance	209 (22%)	48 (18%)	109 (25%)	187 (21%)
PTD	150 (16%)	37 (14%)	79 (18%)	144 (17%)

**N* represents the number of study participants having at least one measurement in at least biometric parameter within the gestational age category under consideration.

Table 2. Frequency of Adverse Outcome with Biometry Differences (CRL and AC) in all twins.

Parameter and Gestational Age	Event	Composite adverse perinatal outcome	18% BW discordance	PTD
CRL from 11 + 0 to 14 + 0 weeks	>20%	50% (1/2)	50% (1/2)	50% (1/2)
	<20%	13% (33/252)	18% (47/258)	13% (35/258)
	Adjusted HR 95% CI	0.1–2.1	0.1–2.3	0.1–2.3
AC from 14 + 1 to 17 + 6 weeks	>10%	31% (21/67)	42% (28/67)	37% (25/67)
	<10%	22% (82/365)	22% (79/365)	17% (61/365)
	Adjusted HR 95% CI	0.9-3.0	1.3–3.9*	1.2–3.9*
AC from 18 + 0 to 21 + 6 weeks	>10%	45% (49/109)	43% (47/109/)	37% (40/109/)
	<10%	22% (211/951)	20% (188/951)	16% (154/951)
	Adjusted HR 95% CI	1.5–3.4***	2.0–4.8***	1.5–3.8***

Abbrevations: CO = Composite Outcome, BW = Birthweight discordance, PTD = Pre-term delivery (<34 weeks), HR = Hazard Ratio, NE = Non-estimable.

Composite outcome defined as any: Death, IVH, HIE, PVL, NEC, RDS or Sepsis.

Adjusted HR 95% CI is adjusted for chorionicity, maternal age, BMI, cord insertion site (central/non-central) and assisted reproductive therapy yes/no).

*$p < 0.05$, ***$p < 0.0001$ and statistically significant after adjustment for multiple comparisons.

Table 3. Frequency of Adverse Outcome with Biometry Differences (FL, EFW and BPD) in all twins.

Parameter and gestational age	Event	Composite adverse perinatal outcome	18% BW discordance	PTD
FL from 14 + 1 to 17 + 6 weeks	>10%	28% (30/107)	32% (34/107)	26% (28/107)
	<10%	21% (76/365)	22% (82/365)	16% (60/365)
	Adjusted HR 95% CI	1.1–2.8*	1.5–4.4***	0.9–2.8
FL from 18 + 0 to 21 + 6 weeks	>10%	32% (35/108)	36% (39/108)	26% (28/108)
	<10%	23% (223/962)	21% (199/962)	17% (163/962)
	Adjusted HR 95% CI	0.7–2.0	01.1–2.7*	0.9–2.8
EFW from 14 + 1 to 17 + 6 weeks	>10%	75% (3/4)	50% (2/4)	50% (2/4)
	<10%	30% (3/10)	20% (2/10)	30% (3/10)
	Adjusted HR 95% CI	NE	NE	0.5–14
EFW from 18 + 0 to 21 + 6 weeks	>10%	40% (61/151)	38% (57/151)	30% (45/151)
	<10%	22% (69/308)	17% (52/308)	14% (43/308)
	Adjusted HR 95% CI	1.3–2.9*	1.7–4.4*	1.4–3.7*
BPD from 14 + 1 to 17 + 6 weeks	>10%	36% (13/36)	39% (14/36)	42% (15/36)
	<10%	21% (95/444)	23% (104/444)	17% (74/444)
	HR 95% CI	0.9–3.7	1.1–4.9*	1.3–5.5*
BPD from 18 + 0 to 21 + 6 weeks	>10%	36% (20/55)	51% (28/55)	31% (17/55)
	<10%	24% (240/1017)	21% (211/1017)	17% (176/1017)
	Adjusted HR 95% CI	1.1–3.3*	1.7–5.0***	1.3–4.5*

Abbrevations: CO = Composite Outcome, BW = Birthweight discordance, PTD = Pre-term delivery (<34 weeks), HR = Hazard Ratio, NE = Non-estimable.
Composite outcome defined as any: Death, IVH, HIE, PVL, NEC, RDS or Sepsis.
Adjusted HR 95% CI is adjusted for chorionicity, maternal age, BMI, cord insertion site (central/non-central) and assisted reproductive therapy yes/no).
*$p < 0.05$, ***$p < 0.0001$ and statistically significant after adjustment for multiple comparisons.

and of PTD amongst all twins and DC twins (p value <0.05, not statistically significant after the Bonferroni correction). Inter-twin differences in AC did not demonstrate a predictive ability for MC twins at this gestational age.

Between 18 and 22 weeks >10% difference in AC was predictive for the overall twin cohort, DC twins and MC twins of composite perinatal morbidity, birthweight discordance of 18% or greater and of PTD. Prediction was strongest for MC twins.

Discussion

In this study we found a strong correlation between fetal AC discordance in the early second trimester (prior to 22 weeks) and perinatal risk in both monochorionic and dichorionic twins. First trimester inter-twin CRL difference was not predictive of perinatal outcome in our study, however only 26% of the cohort had CRL recorded, therefore the study was underpowered to assess this outcome. The lack of early ultrasounds is a limitation of this study as it may have potentially led to inaccurate dating. Deter et al. explored the importance of first trimester growth and identified it as being potentially useful at predicting growth abnormalities [13]. More recently the relationship between first trimester CRL and birthweight in pregnancies conceived through IVF (where the true gestational age was known) was examined. Their results showed that birthweight was significantly greater in babies with larger CRL [14]. Findings for singleton pregnancies have been echoed in twins. Differences in CRL may represent the separate genetic potential of each fetus in dizygotic twins or may reflect the uneven early division of the cell mass in monozygotic twins [8].

Several studies have suggested a strong relationship between CRL and subsequent birthweight discordance [4,15]. Indeed, it has also been suggested that CRL discrepancies of greater that 10% increase the risk of fetal structural and chromosomal anomalies [16], however this study focused on fetal anomalies and fetal loss and did not comment specifically on PTD or other adverse outcomes that we have examined in our study.

Nuchal translucency (NT) has also been shown to be of use in monochorionic twins, however it was not recorded in our study group. NT in conjunction with CRL measurements in monochorionic twins was used to investigate the incidence of abnormal first-trimester ultrasound measurements and their correlation with the outcome of monochorionic diamniotic pregnancies. They found that monochorionic twin gestations that ultimately develop twin–twin transfusion syndrome may exhibit intertwin difference in growth as early as 11–14 weeks of gestation. Furthermore, it showed that the earlier the discordance is identified, the earlier the development of the disease [17]. In addition to these findings it has been shown that intertwin discordance in CRL, heart rate and gestational sac diameter between 6 and 10 weeks gestation were significantly associated with the intrauterine death of one twin [18].

Other studies however have failed to show a significant relationship between first trimester ultrasound and birthweight discordance [19]. Overall, the use of CRL as a predictor of adverse perinatal outcome has had varying degrees of success. In a recent review article the authors did not find CRL to be a reliable predictor of birthweight discordance, suggesting that growth potential is not determined entirely in the first trimester and that the identification of CRL discordance is not a reliable substitute for serial assessment of growth trajectories [20].

The Royal College of Obstetricians and Gynaecologists advocates regular ultrasound evaluation in MC twins from

16 weeks onwards every 2–3 weeks and places particular importance on the AC measurements [21]. A study in 2005 highlighted the importance of AC difference in 503 DC twins until 38 weeks gestation. They demonstrated that an inter-twine AC ratio of <0.93 was highly predictive of birthweight discordance [5].

In our study we found the AC after 14 weeks to be the single most important parameter in the prediction of adverse outcome. AC measurements were found to be more predictive than other growth parameters such as estimated fetal weight, biparietal diameter and femur length. In our cohort, this association was strongest between 18 and 22 weeks but was evident from 14 weeks onwards. This strong relationship may be explained in part by the fact that a small AC is likely to suggest placental insufficiency, leading to iatrogenic PTD which is likely to be responsible for some of the prematurity-related complications.

A recent study of 661 twin pairs compared the efficacy of estimated fetal weight and AC ratio difference of 1.3 or greater as predictors of birthweight discordance and found AC to have a high sensitivity and specificity [22]. AC discordance ratio of 0.93 has been proven to be a useful predictor of birthweight discordance at any gestation [5]. It has also been shown that AC discordance at 16 weeks is predictive of a complicated fetal outcome (defined as TTTS, severe growth discordance or fetal death) [23]. There is evidence in the literature to support estimated fetal weight (EFW) as early as the second trimester as an accurate predictor of birthweight discordance [24]. However, most studies in the literature are concerned with estimated fetal weights in the third trimester. To account for the multiple testing of different outcomes for each of the biometric parameters for each gestational age range, all statistical analyses were adjusted using the Bonferroni Correction thereby minimizing the possibility of presenting false-positive conclusions. The use of these statistical methods allowed us to tease out the relative contributions of BPD, FL, AC and EFW to pregnancy outcome.

Overall there is evidence in the literature to support the use of the AC as a predictor of adverse outcome. However, the majority of studies in the literature to date have not looked specifically at preterm labor or other composite adverse outcomes that we have delineated in our study. A further merit of our study is its large size and further refinement of the utility of biometric parameters in predicting adverse outcome by analyzing results according to specific gestational time frames.

This study is further strengthened by consistent use of similar equipment in all participating centers, a standardized protocol for the frequency of ultrasound surveillance, complete ascertainment of neonatal data for all study participants, regular quality control systems in place and contemporaneous data storage in a centralized database.

While first trimester biometry was not useful for predicting adverse outcome, we have demonstrated that biometry in the early second trimester, prior to 22 weeks gestation, can successfully identify twin pregnancies at an increased risk of poor perinatal outcome.

Intertwin AC difference of greater than 10% between 18 and 22 weeks gestation was the best individual predictor of perinatal risk in both monochorionic and dichorionic twins. Sonographic biometry in twins as early as 14 weeks in both MC and DC twins can be clinically useful by allowing clinicians to better counsel parents and tailor antenatal care according to risk. The recognition of the importance of ultrasound early in the second trimester therefore could potentially improve patient care and ultimately perinatal outcome.

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Declaration of interest

The authors report no conflict of interest.

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