Patterns of second- and third-trimester growth and discordance in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort

Mr Oliver T. STIRRUP MSc*, Asma KHALIL MD†, Francesco D'ANTONIO MD† and Prof Baskaran THILAGANATHAN MD†, on behalf of the Southwest Thames Obstetric Research Collaborative (STORK)

*MRC Clinical Trials Unit at UCL, University College London, London, UK; †Fetal Medicine Unit, Division of Developmental Sciences, St George's University of London, London, UK

Correspondence to: Mr O. Stirrup, MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London, WC2B 6NH (e-mail: oliver.stirrup.13@ucl.ac.uk)

Short title:

Patterns of intertwin discordance

ABSTRACT

Introduction: This study investigates patterns of intertwin size discordance in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies.

Material and Methods: Ultrasound measurements of twin pregnancies, from 14 weeks to term, were collected by nine hospitals over a 10-year period. This analysis considers the modelled and observed levels of discordance in abdominal circumference (AC) and estimated fetal weight (EFW) in relation to gestational age. Fitted models were analyzed to produce charts displaying the expected range of intertwin discordance in AC and EFW at any given examination.

Results: The dataset for analysis included a total of 9866 ultrasound examinations in 1802 DCDA and 323 MCDA twin pregnancies. The 95th percentile of intertwin discordance in EFW increased from 18.3% (95% CI, 17.8–18.7%) at 20 weeks to 21.9% (95% CI, 21.3–22.4%) at 30 weeks for DCDA pregnancies. The 95th percentile for intertwin discordance in AC was stable at 10–11% for this period. Slightly higher levels of discordance were observed for MCDA than for DCDA pregnancies.

Discussion: The expected range of intertwin discordance in EFW and AC shows differences with gestational age and between DCDA and MCDA pregnancies.

Key words: fetal growth; intertwin discordance; multiple pregnancy; twin pregnancy; ultrasound

INTRODUCTION

Ultrasound measurements of fetal biometry are used to identify and monitor the development of pregnancies with abnormal growth, associated with a higher risk of adverse pregnancy outcome. Twin pregnancies are affected by higher rates of complications than singleton pregnancies and so are managed with relatively increased prenatal surveillance, including serial ultrasound scans for the assessment of fetal well-being and growth [1,2]. As for singleton pregnancies, each individual fetus in a twin pregnancy can be assessed in comparison to growth standards for uncomplicated pregnancies [2], but their development may be better assessed by the evaluation of intertwin differences.

The presence of a large discrepancy in birth weight between twins has been shown to be strongly associated with adverse pregnancy outcome [3], and size discordance on ultrasound examination is therefore used as an indicator for pathological growth restriction. The UK National Institute for Health and Clinical Excellence (NICE) guidelines for the clinical management of multiple pregnancy state that a 25% or greater difference in size between twins should be considered to be a clinically important indicator of intrauterine growth restriction (IUGR), and that referral to a tertiary level fetal medicine center should be offered when this finding is observed [1]. The American College of Obstetricians and Gynecologists practice bulletin on multiple gestation considers a reduction of 15–25% in the estimated fetal weight (EFW) of the smaller twin as compared to the larger to constitute discordant fetal growth [4]. A recent study carried out by the Perinatal Ireland Research Consortium found that a cut-off of 18% for discordance in birth weight optimally predicted adverse outcome, and hence suggested that this value should be used to identify pregnancies that require more intensive fetal monitoring [3].

A recent review, summarising studies including over one million twin pregnancies, found a prevalence of birth weight discordance ≥20% of 16%, with 5% of pregnancies having a discordance of ≥30% [5]. However, it is not known how discrepancies in individual fetal biometric measurements or EFW would be expected to vary across gestation, as previous studies have for the most part just analyzed the association between set cut-off values for percentage discordance and poor outcome. The aim of the present study was to investigate patterns of intertwin discordance in abdominal circumference (AC) and EFW across the second and third trimesters in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies.

METHODS

The dataset for this study comprises serial biometric measurements in twin pregnancies collected by nine hospitals in the Southwest Thames region of England between 2001 and 2010 as part of a retrospective cohort study by the Southwest Thames Obstetric Research Collaborative (STORK). Ethical approval was not required for this retrospective study as determined by the local institutional review board guidance.

This analysis focuses on fetal AC and EFW obtained from 14 weeks' gestation onwards in the second and third trimesters in DCDA and MCDA twin pregnancies. The criteria for inclusion in the analysis were as previously described [(6)]. Briefly, gestational age was determined by measurement of crown–rump length of the larger twin in the first-trimester, with pregnancies for which this was not available excluded. Pregnancies in which the chorionicity and amnionicity were uncertain or inconsistent in the recorded examinations were also excluded. This is an analysis of fetal growth in an unselected cohort that was subject to modern clinical management, without any exclusions relating to pregnancy outcome or pathology.

For measurement occasions at which AC, femur length (FL) and head circumference (HC) were recorded, the estimated fetal weight was calculated using the following formula published by Hadlock *et* al. [(7)]:

$$\text{Log}_{10}(\text{EFW}) = 1.326 - 0.00326*\text{AC}*\text{FL} + 0.0107*\text{HC} + 0.0438*\text{AC} + 0.158*\text{FL}$$

Analysis of discordance was conducted with respect to the intertwin difference expressed as a percentage of the value for the larger twin for EFW and AC, and absolute discordance in AC was also investigated.

Statistical Analysis

Multilevel mixed effects statistical models were used to evaluate growth in AC and EFW in relation to gestational age. The modelling strategy has been described in detail in a previous paper [(6),] for which the same fitted model for AC was analyzed as in the present study. A detailed description of the modelling strategy and a summary of the fitted models for AC are also provided in Appendix S1 of this paper. The models fitted for EFW have not been previously reported in any form.

Separate models for each variable were constructed for DCDA and MCDA pregnancies, in order to allow differences between them in both the mean and covariance structure. Gestational age was expressed in weeks and centred at 14 weeks, meaning that the 'intercept' term in each model corresponds to values at this gestational age. All models were fit using MLwiN (Version 2.28; Centre for Multilevel Modelling, University of Bristol, Bristol, UK).

The distribution for the difference in EFW and in AC measurements between the two twin fetuses at any one examination across gestation from 14–40 weeks was derived from the fitted models for DCDA and MCDA pregnancies. For absolute differences in AC, this was achieved analytically using a half normal distribution. The distributions for percentage differences in AC and EFW, relative to the value for the larger twin, were also calculated. For EFW, this could be achieved analytically (following from the fact that the variable was modelled on the log-scale), but for AC the distribution of percentage differences was found by randomly generating data for one million simulated examinations for each week of gestational age based on the fitted model. This was carried out using the 'MASS' package in R (Version 3.1.0; R Foundation, Vienna, Austria). Confidence intervals for reported percentiles of EFW discordance % were calculated using the standard errors of covariance parameters and the delta method.

The fit of percentiles for intertwin discordance in AC and EFW with respect to gestational age were checked by comparison to plots of the observed differences for each individual examination in the dataset that had AC or EFW values recorded for both twins. Quantile regression was also applied to the observed values in order to provide confirmation of the appropriate fit of the model-based percentiles. This was done using the 'stat_quantile' option for the 'ggplot2' (Version 0.9.3.1) package in R, which calls the 'quantreg' package (Version 5.05), and the number of splines was set at five to allow a smooth fit to the data.

RESULTS

The initial raw dataset contained examination records for 2540 DCDA, 429 MCDA and 39 MCMA pregnancies, with an additional 275 pregnancies in which the chorionicity and amnionicity were uncertain or inconsistent. Applying the condition that at least one examination be present in the dataset with measurements recorded for both fetuses beyond 14 weeks led to the exclusion of 446 DCDA and 56 MCDA pregnancies, and the condition that at least one scan prior to 14 weeks be recorded led to the exclusion of a further 292 DCDA and 50 MCDA pregnancies, yielding 1802 DCDA and 323 MCDA pregnancies for inclusion in the analysis. There were records of 9866 separate examinations beyond 14 weeks for the included pregnancies and, out of the total potential measurements for each fetus at each examination, 98.6% were present for AC and EFW could be calculated for 93.0%.

Full details of the fitted statistical model for AC have been published previously [(6)]. In line with the individual biometric variables, the best-fitting model for $\log_{10}$(EFW) was a quadratic function in terms of gestational age for both DCDA and MCDA pregnancies. The examination-specific variance (on the log scale) was not found to increase with gestational age in either case. Six DCDA pregnancies and one MCDA pregnancy were excluded from the final model fits because of extreme residual values (Z-scores of >6). Full details of the fitted models for $\log_{10}$(EFW) are given in Appendix S2. Reference ranges for EFW in DCDA and MCDA pregnancies derived from the models are displayed in Figure 1, with values also provided in Table S1 and shown with raw data in Figure S1. These show the 95th percentile of EFW to be similar between DCDA and MCDA pregnancies across gestation, but that the 5th and 50th percentiles are lower in MCDA cases.

From the model-based analysis, the 95th percentile of intertwin discordance in EFW at any given examination increased steadily from 18.3% (95% CI, 17.8–18.7%) at 20 weeks to 21.9% (21.3–22.4%) at 30 weeks for DCDA pregnancies (Figure 2a, Table S2). A similar trend, but with slightly higher respective values of 22.2% (20.9–23.4%) and 25.4% (23.9–27.0%) was observed for MCDA pregnancies (Figure 2c, Table S3). There was close agreement between the model-based analysis and the quantiles fitted to the raw data up until around 33 weeks for DCDA (Figure 2b) and 30 weeks for MCDA (Figure 2d) pregnancies. The divergence beyond these time points suggests that lower levels of discordance are observed in practice closer to term than are predicted by the fitted statistical models. A similar pattern of observations was found for the percentage discordance in AC (Figure 3), although the percentiles were more stable between 20 and 30 weeks.

The percentiles for absolute discordance in AC were found to increase steadily from about 16 weeks, with equivalent values slightly higher in MCDA than in DCDA pregnancies (Figure 4, Table S2 and S3). As for EFW, inspection of the raw data indicated that lower levels of intertwin discordance are present beyond around 33 weeks than predicted by the fitted statistical models.

DISCUSSION

Main findings

One of the most important findings of this study is that the percentiles of intertwin discordance in EFW and AC vary with gestational age. Furthermore, the magnitude of intertwin discordance in both EFW and AC were found to be in general larger in MCDA pregnancies than in DCDA pregnancies. These findings suggest that the performance of gestation- and chorionicity-dependant, variable cut-offs for the detection of clinically relevant intertwin discordance should be further investigated.

The degree of intertwin discordance in EFW is often used to identify pregnancies in which there is abnormal growth, with commonly recommended cut-offs of 20% [(2)] or 25% [(1)]. One study found that a cut-off of 18% for discordance in birth weight optimally predicted adverse outcome, and hence suggested that this lower value should be used [(3)]. The present analysis indicates that using such fixed cut-offs, even when expressed as a percentage rather than absolute discordance, will select different proportions of pregnancies as being high-risk depending on the chorionicity and gestational age at examination considered. For example, the model developed predicts that a 20% cut-off for intertwin discordance in EFW would select 3.0% of DCDA pregnancies at 20 weeks but 7.6% at 30 weeks, and for MCDA pregnancies the proportions would be 8.1% and 13.6%, respectively. One guidelines document, published by the Society of Obstetricians and Gynaecologists of Canada, suggests that an absolute difference in AC of greater than 20 mm can be used to define abnormal growth discordance [(2)]. However, considering DCDA pregnancies, the present analysis demonstrates that this cut-off varies from being equivalent to the 98^{th} percentile at 20 weeks to being only around the 83^{rd} percentile at 30 weeks. The percentiles for percentage discordance in AC are much more stable across gestation, at least beyond around 20 weeks.

Strengths and limitations

The strengths of this study include the analysis of a large dataset of fetal biometry data obtained in clinical practice and the use of statistical models that appropriately account for the nested structure of the data, with multiple observations per fetus and associations between the growth profiles of the two fetuses within each twin pregnancy. The use of multilevel statistical models provides some protection against the potential for more frequent observations in complicated pregnancies to bias the analysis, as an abnormal fetus (or pair of fetuses) is effectively treated as a single abnormal trajectory within the model rather than each observation being treated as independent. However, it is important to note that there were substantial discrepancies between the percentiles predicted by the statistical models and those obtained through the more direct application of quantile regression to the observed data.

Assuming that their structure has been correctly specified, the statistical mixed effects models used in this study have a degree of robustness to missing data. This is an important quality when dealing with a dataset with highly variable number and timing of observations per individual as is the case in this analysis. However, the calculation of percentiles of intertwin discordance based on these statistical models implicitly makes the assumption that the timing of delivery is not related in any way to the variable under consideration. Hence the model-based percentiles can be interpreted as relating to a hypothetical population of pregnancies in which there are no deliveries prior to full term. This assumption is of course problematic, particularly given the high rate of preterm delivery in twin pregnancies, with one large study reporting delivery before 37 weeks in 41% of DCDA and 56% of MCDA cases [8]. The naïve quantile regression approach does not make such an assumption. However, it does not account for dependency in the data resulting from the inclusion of serial measurements for each individual pregnancy, and as such could be subject to other biases, including the over-representation of abnormal cases with a greater number of follow-up examinations. As such, we believe that the most reliable percentiles are those from the model-based approach, but that these are less reliable beyond 33 weeks in DCDA pregnancies and beyond 30 weeks in MCDA pregnancies. After these points in gestations, the centiles clearly diverge from the observed data, indicating that the raw centiles are more reliable nearer term. Timing of delivery is more likely to be decided on the basis of intertwin discordance near term – thereby leading to a difference between the modelled centiles and those observed in practice.

The fact that there is a divergence between the predictions regarding intertwin discordance made by the fitted models and examination of the observed raw data in the third trimester seems to imply that the magnitude of intertwin discordance is interlinked with the timing of delivery. This is not surprising, as this analysis relates to an unselected cohort in which pregnancies were subject to current clinical management protocols. In this setting, pregnancies demonstrating large intertwin discordance would be likely to be electively delivered.

A further limitation of this study is that it is a retrospective analysis and it was not possible to account for the occurrence of pregnancy complications in the evaluation of intertwin discordance. As such, it was decided to perform an analysis of a completely unselected cohort of twin pregnancies and the percentile values presented therefore reflect a clinically managed population of twin pregnancies. The median EFW for a fetus in a DCDA pregnancy at any given gestational age was correspondingly found to be slightly smaller in the present study in comparison to a recent analysis of non-anomalous fetuses conducted by Shivkumar *et al.* [9]. The study is also limited to investigation of the distribution of intertwin discordance according to chorionicity, without providing further direct insights into differences in the underlying pathophysiology of discordance between these groups [10].

Interpretation

There have been numerous studies that have demonstrated an association between intertwin discordance in birth weight and perinatal mortality and morbidity [11,12,13,3]. However, there is less evidence regarding whether intertwin discordance in fetal size at ultrasound examination is predictive of adverse outcomes, or even of discordance in birth weight. Diaz-Garcia *et al*. [14] and Hoopmann *et al*. [15] reported that EFW on ultrasound examination within 15 or 14 days prior to delivery is predictive of birth weight discordance, but with a sensitivity of only around 60% for a 10% false-positive rate when considering a discordance of ≥25%. Hoopmann *et al.* (15) also found that EFW at 18–25 weeks was poorly predictive of birth weight discordance. A study by van de Waarsenburg *et al.* found that an EFW discordance of ≥20% at last ultrasound before delivery gave a sensitivity of 57% and specificity of 94% for an equivalent birth weight discordance [16].

The STORK cohort analysed in the present study has also been the subject of two previous papers relating to intertwin discordance in the second and third trimesters. One of these studies evaluated the predictive performance of intertwin percentage discordance in EFW at 20–22 weeks, after exclusion of cases with structural or chromosomal abnormalities, finding that the degree of discordance at this point in pregnancy was not associated with fetal loss, preterm delivery <34 weeks or perinatal loss [(17)]. However, a birth weight discordance of ≥25% was found to be strongly associated with perinatal loss, as was an EFW discordance of ≥25% at the last ultrasound examination prior to delivery, with most perinatal losses occurring with delivery beyond 30 weeks [(18)]. These findings indicate that further research is required into the associations between intertwin discordance, adverse outcomes and timing of delivery in the third trimester, in order to be able to determine the optimal method for identification of high-risk pregnancies.

CONCLUSION

This study has demonstrated that the percentiles of intertwin discordance in AC and EFW at any one examination vary with gestational age, and also differ between DCDA and MCDA pregnancies. These findings are relevant when considering whether to choose a set cut-off point for the identification of high-risk pregnancies. Importantly, the percentiles generated from fitted statistical models do not seem to reflect the observed distribution of intertwin discordance close to term because of data censoring from elective delivery, and further investigation is needed regarding growth patterns in this period in pregnancy.

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STORK contributors

Arash Bahamie, St Peter's Hospital

Amar Bhide, St George's University of London

Anne Deans, Frimley Park Hospital

Michael Egbor, St Helier's Hospital

Hina Gandhi, East Surrey Hospital

Heather Allen-Coward, Mayday University Hospital

Renata Hutt, Royal Surrey County Hospital

Adetunji Matiluko, St Helier's Hospital

Kim Morgan, Frimley Park Hospital

Faz Pakarian, Worthing Hospital

Aris Papageorghiou, St George's University of London

Elisabeth Peregrine, Kingston Hospital

Lesley Roberts, Royal Surrey County Hospital

Conflict of interest:

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FIGURE LEGENDS

Figure 1 Plots of 5th, 50th and 95th percentiles (—) of estimated fetal weight (EFW) as a function of gestational age in dichorionic diamniotic (black lines) and monochorionic diamniotic (blue lines) twin pregnancies. The values are derived from the statistical models for Log_{10}(EFW). 95% CIs are shown for the 50th percentile (·····).

Figure 2 Plots of 50th (—), 90th (– – –), 95th (·–·–·) and 99th (·····) percentiles of intertwin discordance in estimated fetal weight (EFW) as a percentage of the value in the larger twin, with respect to gestational age, in dichorionic diamniotic (a,b) and monochorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile values derived from the fitted statistical models, whilst (b) and (d) show results of quantile regression applied to the raw data for each examination (●) without taking account of the serial nature of measurements.

Figure 3 Plots of 50th (—), 90th (– – –), 95th (·–·–·) and 99th (·····) percentiles of intertwin discordance in abdominal circumference (AC) as a percentage of the value in the larger twin, with respect to gestational age, in dichorionic diamniotic (a,b) and monochorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile values derived from the fitted statistical models, whilst (b) and (d) show results of quantile regression applied to the raw data for each examination (●) without taking account of the serial nature of measurements.

Figure 4 Plots of 50th (—), 90th (– – –), 95th (·–·–·) and 99th (·····) percentiles of absolute intertwin discordance in abdominal circumference (AC), with respect to gestational age, in dichorionic diamniotic (a,b) and monochorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile values derived from the fitted statistical models, whilst (b) and (d) show results of quantile regression applied to the raw data for each examination (●) without taking account of the serial nature of measurements.

SUPPLEMENTARY MATERIAL

Figure S1 Plots of raw data (●) and 5th, 50th and 95th percentiles (—) of estimated fetal weight (EFW) as a function of gestational age in (a) dichorionic diamniotic and (b) monochorionic diamniotic twin pregnancies. The percentile values are derived from the statistical models for Log_{10}(EFW). 95% CIs are shown for the 50th percentile (·····).

Table S1 Mean and overall standard deviation (i.e. including 'true' differences between fetuses and measurement error) of log-transformed estimated fetal weight (EFW) and 5th, 50th and 95th percentiles (P5, P50 and P95) of EFW derived from the fitted statistical models in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies

Table S2 50th, 90th, 95th and 99th percentiles (P50, P90, P95 and P99) of intertwin differences in estimated fetal weight (EFW) and abdominal circumference (AC) in dichorionic diamniotic twin pregnancies between 14 and 33 weeks. The values are derived from the fitted statistical models and include the estimated 'true' differences between fetuses and measurement error. Percentage differences are given relative to the value for the larger twin. The values calculated do not appear to match those observed in practice beyond 33 weeks.

Table S3 50th, 90th, 95th and 99th percentiles (P50, P90, P95 and P99) of intertwin differences in estimated fetal weight (EFW) and abdominal circumference (AC) in monochorionic diamniotic twin pregnancies between 14 and 30 weeks. The values are derived from the fitted statistical models and include the estimated 'true' differences between fetuses and measurement error. Percentage differences are given relative to the value for the larger twin. The values calculated do not appear to match those observed in practice beyond 30 weeks.

Appendix S1 Details of the statistical modelling strategy used and of parameter estimates of the fitted models for abdominal circumference, as previously reported [(6)].

Appendix S2 Details of the statistical models fitted for estimated fetal weight as a function of gestational age in dichorionic diamniotic and monochorionic diamniotic twin pregnancies.