

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

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

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

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

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17 **Short title:**

18 Patterns of intertwin discordance

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1 **ABSTRACT**

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

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

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

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

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

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1 INTRODUCTION

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

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

21 A recent review, summarising studies including over one million twin pregnancies, found a prevalence of birth
22 weight discordance $\geq 20\%$ of 16%, with 5% of pregnancies having a discordance of $\geq 30\%$ ⁽⁵⁾. However, it is not
23 known how discrepancies in individual fetal biometric measurements or EFW would be expected to vary across
24 gestation, as previous studies have for the most part just analyzed the association between set cut-off values for
25 percentage discordance and poor outcome. The aim of the present study was to investigate patterns of

1 intertwin discordance in abdominal circumference (AC) and EFW across the second and third trimesters in
2 dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies.

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1 METHODS

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

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

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

$$15 \text{Log}_{10}(\text{EFW}) = 1.326 - 0.00326 * \text{AC} * \text{FL} + 0.0107 * \text{HC} + 0.0438 * \text{AC} + 0.158 * \text{FL}$$

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

18 *Statistical Analysis*

19 Multilevel mixed effects statistical models were used to evaluate growth in AC and EFW in relation to
20 gestational age. The modelling strategy has been described in detail in a previous paper⁽⁶⁾, for which the same
21 fitted model for AC was analyzed as in the present study. A detailed description of the modelling strategy and a

1 summary of the fitted models for AC are also provided in Appendix S1 of this paper. The models fitted for EFW
2 have not been previously reported in any form.

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

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

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

1 RESULTS

2 The initial raw dataset contained examination records for 2540 DCDA, 429 MCDA and 39 MCMA pregnancies,
3 with an additional 275 pregnancies in which the chorionicity and amnionicity were uncertain or inconsistent.
4 Applying the condition that at least one examination be present in the dataset with measurements recorded for
5 both fetuses beyond 14 weeks led to the exclusion of 446 DCDA and 56 MCDA pregnancies, and the condition
6 that at least one scan prior to 14 weeks be recorded led to the exclusion of a further 292 DCDA and 50 MCDA
7 pregnancies, yielding 1802 DCDA and 323 MCDA pregnancies for inclusion in the analysis. There were records of
8 9866 separate examinations beyond 14 weeks for the included pregnancies and, out of the total potential
9 measurements for each fetus at each examination, 98.6% were present for AC and EFW could be calculated for
10 93.0%.

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12 Full details of the fitted statistical model for AC have been published previously⁽⁶⁾. In line with the individual
13 biometric variables, the best-fitting model for $\log_{10}(\text{EFW})$ was a quadratic function in terms of gestational age
14 for both DCDA and MCDA pregnancies. The examination-specific variance (on the log scale) was not found to
15 increase with gestational age in either case. Six DCDA pregnancies and one MCDA pregnancy were excluded
16 from the final model fits because of extreme residual values (Z-scores of >6). Full details of the fitted models for
17 $\log_{10}(\text{EFW})$ are given in Appendix S2. Reference ranges for EFW in DCDA and MCDA pregnancies derived from
18 the models are displayed in Figure 1, with values also provided in Table S1 and shown with raw data in Figure
19 S1. These show the 95th percentile of EFW to be similar between DCDA and MCDA pregnancies across gestation,
20 but that the 5th and 50th percentiles are lower in MCDA cases.

21
22 From the model-based analysis, the 95th percentile of intertwin discordance in EFW at any given examination
23 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
24 pregnancies (Figure 2a, Table S2). A similar trend, but with slightly higher respective values of 22.2% (20.9–
25 23.4%) and 25.4% (23.9–27.0%) was observed for MCDA pregnancies (Figure 2c, Table S3). There was close

1 agreement between the model-based analysis and the quantiles fitted to the raw data up until around 33 weeks
2 for DCDA (Figure 2b) and 30 weeks for MCDA (Figure 2d) pregnancies. The divergence beyond these time points
3 suggests that lower levels of discordance are observed in practice closer to term than are predicted by the fitted
4 statistical models. A similar pattern of observations was found for the percentage discordance in AC (Figure 3),
5 although the percentiles were more stable between 20 and 30 weeks.

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

1 DISCUSSION

2 Main findings

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

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

22 Strengths and limitations

23 The strengths of this study include the analysis of a large dataset of fetal biometry data obtained in clinical
24 practice and the use of statistical models that appropriately account for the nested structure of the data, with

1 multiple observations per fetus and associations between the growth profiles of the two fetuses within each
2 twin pregnancy. The use of multilevel statistical models provides some protection against the potential for more
3 frequent observations in complicated pregnancies to bias the analysis, as an abnormal fetus (or pair of fetuses)
4 is effectively treated as a single abnormal trajectory within the model rather than each observation being
5 treated as independent. However, it is important to note that there were substantial discrepancies between the
6 percentiles predicted by the statistical models and those obtained through the more direct application of
7 quantile regression to the observed data.

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

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

6 A further limitation of this study is that it is a retrospective analysis and it was not possible to account for the
7 occurrence of pregnancy complications in the evaluation of intertwin discordance. As such, it was decided to
8 perform an analysis of a completely unselected cohort of twin pregnancies and the percentile values presented
9 therefore reflect a clinically managed population of twin pregnancies. The median EFW for a fetus in a DCDA
10 pregnancy at any given gestational age was correspondingly found to be slightly smaller in the present study in
11 comparison to a recent analysis of non-anomalous fetuses conducted by Shivkumar *et al.*⁽⁹⁾. The study is also
12 limited to investigation of the distribution of intertwin discordance according to chorionicity, without providing
13 further direct insights into differences in the underlying pathophysiology of discordance between these groups
14 ⁽¹⁰⁾.

15 Interpretation

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

1 The STORK cohort analysed in the present study has also been the subject of two previous papers relating to
2 intertwin discordance in the second and third trimesters. One of these studies evaluated the predictive
3 performance of intertwin percentage discordance in EFW at 20–22 weeks, after exclusion of cases with
4 structural or chromosomal abnormalities, finding that the degree of discordance at this point in pregnancy was
5 not associated with fetal loss, preterm delivery <34 weeks or perinatal loss⁽¹⁷⁾. However, a birth weight
6 discordance of $\geq 25\%$ was found to be strongly associated with perinatal loss, as was an EFW discordance of
7 $\geq 25\%$ at the last ultrasound examination prior to delivery, with most perinatal losses occurring with delivery
8 beyond 30 weeks⁽¹⁸⁾. These findings indicate that further research is required into the associations between
9 intertwin discordance, adverse outcomes and timing of delivery in the third trimester, in order to be able to
10 determine the optimal method for identification of high-risk pregnancies.

11 **CONCLUSION**

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

18

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22

23 **STORK contributors**

24 Arash Bahamie, St Peter's Hospital

- 1 Amar Bhide, St George's University of London
- 2 Anne Deans, Frimley Park Hospital
- 3 Michael Egbor, St Helier's Hospital
- 4 Hina Gandhi, East Surrey Hospital
- 5 Heather Allen-Coward, Mayday University Hospital
- 6 Renata Hutt, Royal Surrey County Hospital
- 7 Adetunji Matiluko, St Helier's Hospital
- 8 Kim Morgan, Frimley Park Hospital
- 9 Faz Pakarian, Worthing Hospital
- 10 Aris Papageorghiou, St George's University of London
- 11 Elisabeth Peregrine, Kingston Hospital
- 12 Lesley Roberts, Royal Surrey County Hospital
- 13

1 **Conflict of interest:**

2 The authors report no conflict of interest.

3

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1 **FIGURE LEGENDS**

2 **Figure 1** Plots of 5th, 50th and 95th percentiles (—) of estimated fetal weight (EFW) as a function of gestational
3 age in dichorionic diamniotic (black lines) and mono chorionic diamniotic (blue lines) twin pregnancies. The
4 values are derived from the statistical models for $\text{Log}_{10}(\text{EFW})$. 95% CIs are shown for the 50th percentile (.....).

5
6 **Figure 2** Plots of 50th (—), 90th (---), 95th (·-·-·) and 99th (.....) percentiles of intertwin discordance in estimated
7 fetal weight (EFW) as a percentage of the value in the larger twin, with respect to gestational age, in dichorionic
8 diamniotic (a,b) and mono chorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile values derived
9 from the fitted statistical models, whilst (b) and (d) show results of quantile regression applied to the raw data
10 for each examination (●) without taking account of the serial nature of measurements.

11
12 **Figure 3** Plots of 50th (—), 90th (---), 95th (·-·-·) and 99th (.....) percentiles of intertwin discordance in
13 abdominal circumference (AC) as a percentage of the value in the larger twin, with respect to gestational age, in
14 dichorionic diamniotic (a,b) and mono chorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile
15 values derived from the fitted statistical models, whilst (b) and (d) show results of quantile regression applied to
16 the raw data for each examination (●) without taking account of the serial nature of measurements.

17
18 **Figure 4** Plots of 50th (—), 90th (---), 95th (·-·-·) and 99th (.....) percentiles of absolute intertwin discordance in
19 abdominal circumference (AC), with respect to gestational age, in dichorionic diamniotic (a,b) and
20 mono chorionic diamniotic (c,d) twin pregnancies. (a) and(c) show percentile values derived from the fitted
21 statistical models, whilst (b) and (d) show results of quantile regression applied to the raw data for each
22 examination (●) without taking account of the serial nature of measurements.

23

1 SUPPLEMENTARY MATERIAL

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

7

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

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

18 **Table S3** 50th, 90th, 95th and 99th percentiles (P50, P90, P95 and P99) of intertwin differences in estimated fetal
19 weight (EFW) and abdominal circumference (AC) in monochorionic diamniotic twin pregnancies between 14 and
20 30 weeks. The values are derived from the fitted statistical models and include the estimated 'true' differences
21 between fetuses and measurement error. Percentage differences are given relative to the value for the larger
22 twin. The values calculated do not appear to match those observed in practice beyond 30 weeks.

23

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

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

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