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The Impact of Dating Twin Pregnancy by the Larger, Smaller or Mean Twin Crown-Rump Length: A Retrospective Cohort Study

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ABSTRACT

Objective: To evaluate the impact of twin dating by ultrasound-measured crown-rump length (CRL) of the larger (CRL-L), smaller (CRL-S) or mean twin measurement (CRL-M) on the rates of preterm birth (PTB) and detection of small for gestational age (SGA) births.

Design: A retrospective cohort study.

Setting: A tertiary fetal medicine centre (London, UK).

Population or Sample: All twin pregnancies between 1998 and 2023 who underwent first trimester CRL ultrasound assessment and fetal growth assessment.

Methods: Data collection included CRL measurement, estimated fetal weight (EFW), pregnancy outcome and birthweight (BW) for each twin. Pregnancies were retrospectively re-dated by CRL-S, CRL-L and CRL-M.

Main Outcome Measures: SGA < 10th centile and extreme PTB rates (< 28 weeks).

Results: In the 1129 twin pregnancies, median CRL-S was 61 mm (interquartile range [IQR]: 56.0–66.0) and CRL-L was 63 mm (IQR: 58.4–68.9) with a mean discordance of 4.0%. Prenatal SGA diagnosis occurred in 19.8% and 23.1% of smaller twins when dated by CRL-S and CRL-L, respectively. When pregnancies were dated by CRL-M versus CRL-S or CRL-L, there was no difference in prenatal SGA diagnosis ($p = 0.275$ and $p = 0.419$); SGA at birth ($p = 0.132$ and $p = 0.325$); or extreme PTB ($p = > 0.999$ and $p = 0.765$ respectively).

Conclusions: Dating by the smaller, larger or mean twin CRL does not significantly alter rates of extreme preterm birth, SGA detection or SGA birth. Dating by the mean twin CRL reduces stigmatisation of the smaller twin and retains the utility of accurate gestational age assessment without impacting clinical outcomes.

1 | Introduction

Accurate gestational age assessment supports the provision of effective obstetric care and the timing of interventions, including improved detection of fetal growth restriction and estimation of the expected date of birth. It is well established in singleton pregnancies that routine dating based upon first trimester ultrasound crown-rump length (CRL) measurement is more accurate than menstrual dates [1–4]. However, in twin pregnancies, discrepancy between CRL measurements is

common, with a study of 6225 twin pregnancies reporting a median CRL discordance of 3%–4% at 11–14 weeks' gestation, with approximately 1% of twin pregnancies exhibiting a CRL discordance of greater than 20% [5]. The acknowledgment that ultrasound is superior to menstrual dating produces a clinical dilemma when twins are significantly different in size despite being conceived at the same time. Most clinical guidance documents favour the use of the larger twin CRL measurement for ultrasound dating, based on expert consensus rather than evidence of either improved provision of care or better clinical outcomes [6–10].

The reason commonly given for the choice of the larger twin CRL is that dating by the smaller twin CRL will result in systematic underestimation of gestational age and result in a missed diagnosis of fetal growth restriction in later pregnancy. However, a policy of dating by the larger twin CRL will result in the larger twin being plotted in the middle of the CRL reference standard and the co-twin being plotted in the lower centiles and appearing to be already small at 11–14 weeks (Figure 1). This unnecessary stigmatisation of the smaller co-twin, potentially leads to increased antenatal surveillance and heightens anxiety in parents who are already aware that the pregnancy is at increased risk of fetal growth restriction [11–13]. Whilst the converse is true of a policy of dating by the smaller twin, studies supporting this approach are based on small cohorts and do not evaluate the impact on pregnancy outcome [14–17]. An alternative policy of dating by the mean twin CRL has previously been proposed as being both mathematically and biologically appropriate [16]. The aim of this study is to evaluate the impact of various first trimester twin dating strategies on the rates of preterm birth, small for gestational age (SGA) birth and perinatal mortality.

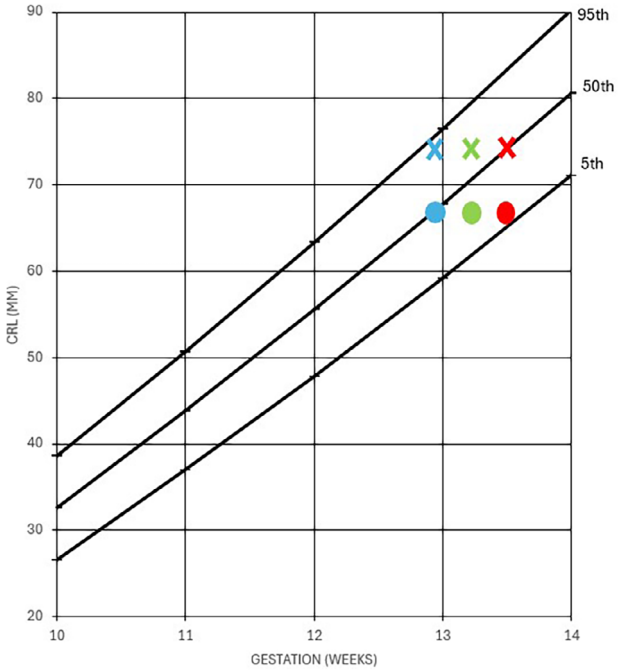

FIGURE 1 | Infographic representation of twin dating by crown-rump length. Crown-rump length (CRL) chart illustrating impact of dating by CRL of larger twin (red), smaller twin (blue) and the mean twin CRL (green). Dating by the CRL of the larger twin (x) causes the smaller twin (•) to fall to the lower centiles. CRL centiles obtained from Intergrowth-21st [https://media.tghn.org/medialibrary/2017/04/GROW_Early_Preg_charts_SIZE_ct_Table.pdf] [assessed 26.02.24].

2 | Methods

This was a retrospective cohort study of all twin pregnancies seen in the Fetal Medicine Unit at St George's University Hospital between May 1998 and May 2023. Women being seen with a twin pregnancy crown-rump length (CRL) measurement at 10–14 weeks gestation and pregnancy outcome available were considered suitable for the analysis. Scan data were obtained by a computerised search of the hospital's obstetric ultrasound computer database (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GmbH, Wessling, Germany), whilst pregnancy outcome details were obtained from the computerised maternity records (EuroKing, Wellbeing Software, Mansfield, UK). These two databases were cross-checked to ensure full data capture of all twin pregnancies during the study period. Exclusion criteria were pregnancies of unknown chorionicity; chromosomal/genetic abnormality; or birth before 24 weeks' gestation. Confirmation was obtained from the research ethics committee that formal ethical approval was not required for this single-centre retrospective study that utilised anonymised and routinely collected data. Main outcome measures were SGA < 10th centile and extreme preterm birth (< 28 weeks).

Data were collected on maternal demographic characteristics, CRL, chorionicity, fetal anomalies, fetal biometry, estimated fetal weight (EFW) based upon last ultrasound prior to birth, pregnancy complications, pregnancy outcome and birthweight (BW). For consistency in labelling during the analysis of the data, the smaller twin was designated as Twin 1 and Twin 2 as the larger twin. Pregnancies were then retrospectively dated by smaller twin CRL (CRL-S), larger twin CRL (CRL-L) and mean twin CRL (CRL-M) using the CRL dating formula by Robinson et al. [18] The impact of the three dating options on ultrasound EFW, rate of SGA < 10th centile at scan or birth and gestational age at birth, were calculated. This allowed determination of the impact of the three different CRL dating options on the accuracy of predicting timing of birth, prenatal SGA detection and SGA rate at birth. CRL discordance (%) was calculated as 100 × (CRL-L − CRL-S)/CRL-L. Ultrasound EFW was calculated using the Hadlock [19] formula based on head circumference, abdominal circumference and femur length, whilst EFW centile was calculated from the INTERGROWTH-21 fetal EFW charts [20]. Birthweight centile was calculated from the INTERGROWTH-21 BW charts [21]. Actual BW discordance (%) was calculated as 100 × (larger BW − smaller BW)/larger BW.

2.1 | Statistical Analysis

Data from categorical variables were expressed as *n* (%) and from continuous variables as median and interquartile range (IQR). A sensitivity analysis demonstrated that chorionicity did not significantly affect any of the outcome variables evaluated and, as such, the monochorionic and dichorionic data were combined to give greater power to the analysis. (Table S1) Categorical data were compared using the chi-square test. The

Mann–Whitney U-test was used to compare continuous data between the study groups (CRL-M vs. CRL-S and CRL-M vs. CRL-L). *p*-values below 0.05 were considered statistically significant. Screening performance of EFW < 10th and < 3rd centiles for the prediction of SGA birth < 10th and < 3rd centiles was expressed using estimates of sensitivity and specificity (%) with 95% confidence intervals. The statistical analysis was performed using SPSS 28.0 (SPSS Inc., Chicago, IL, USA).

3 | Results

A total of 1581 sets of twins were identified using the search criteria, with 452 excluded as they did not fulfil the inclusion criteria (Figure 2). Of the 1129 sets of twins included in the study, 876 were dichorionic and 253 were monochorionic. The maternal demographic and pregnancy characteristics are shown in Table 1.

3.1 | Ultrasound Dating and Gestation at Birth

The CRL distributions and respective gestational ages for CRL-S, CRL-M and CRL-L shown in Table 2 and Figure 3 demonstrate the leftward shift in CRL when using the smaller versus larger twin measurement. When the median CRL was 61 mm (IQR: 56.0–66.0) and 63 mm (IQR: 58.4–68.9) for the smaller and larger twin, the equivalent gestational ages were 12.5 (IQR: 12.2–12.9) and 12.7 weeks (IQR: 12.3–13.1), respectively ($p = < 0.001$ for CRL-S vs. CRL-M and $p = < 0.001$ for CRL-M vs. CRL-L). The mean CRL discordance between twin pairs was 4.0% (1.4 days) with 1.5% ($n = 17$) and 0.5% ($n = 6$) of pregnancies having a CRL discordance of greater than 15% (5.1 days) and 20% (7.7 days), respectively. One twin pair had a CRL discordance of > 25% (25.48%). Median gestational age at birth, when pregnancy dating was based upon CRL-S, CRL-M and CRL-L, was 36.5 (IQR: 34.6–37.3), 36.6 (IQR: 34.7–37.3) and 36.6 (IQR: 34.9–37.4) weeks, respectively (Table 2). There was a significant difference between gestational age at the 11–14-week scan, but not gestation at birth, when pregnancies were dated by CRL-M versus CRL-S or CRL-L (Table 2).

3.2 | EFW Centile and SGA Diagnosis on Ultrasound

At the last scan before birth, the median EFW centile was 33.7% (IQR: 14.3–54.9) and 29.5% (IQR: 12.1–50.3) for the smaller twin when dated by CRL-S and CRL-L, respectively (Table 2). The diagnosis of SGA in the smaller twin was 19.8% and 23.1% when dated by CRL-S and CRL-L, respectively (Table 2). There were no significant differences between median EFW centiles or rates of SGA diagnosis by EFW when pregnancies were dated by CRL-M versus CRL-S or CRL-L. The median duration between the last scan and delivery was 1.29 weeks (IQR: 0.71–2.14).

3.3 | BW Centile and Prevalence of SGA Births

The median BW centile for the smaller twin, when calculated using CRL-S and CRL-L, was 13.2% (IQR: 5.2–28.1) and 11.2% (IQR: 4.2–25.2), respectively (Table 2). The prevalence of SGA birth in the smaller twin was 43.6% and 49.5% when gestation was calculated using CRL-S or CRL-L, respectively. There were no significant differences between median BW centiles or SGA diagnosis by BW when pregnancies were dated by CRL-M versus CRL-S or CRL-L.

3.4 | Twin Size Discordance and Sensitivity of EFW for Predicting SGA Birth

The median EFW discordance between twin pairs was 8.5% (IQR: 4.1–14.2) with 22.5% ($n = 253$) and 7.1% ($n = 80$) of twin pairs having an EFW discordance > 15% and > 25%, respectively. The median BW discordance between twin pairs was 10.1% (IQR: 4.3–17.4) with 32.0% ($n = 292$) and 8.9% ($n = 81$) twin pairs with a BW discordance > 15% and > 25%, respectively. The sensitivity of EFW < 10th centile and < 3rd centile for prediction of SGA birth < 10th or < 3rd centile, respectively, did not vary significantly for pregnancy dating by CRL-S, CRL-M and CRL-L (Table 3).

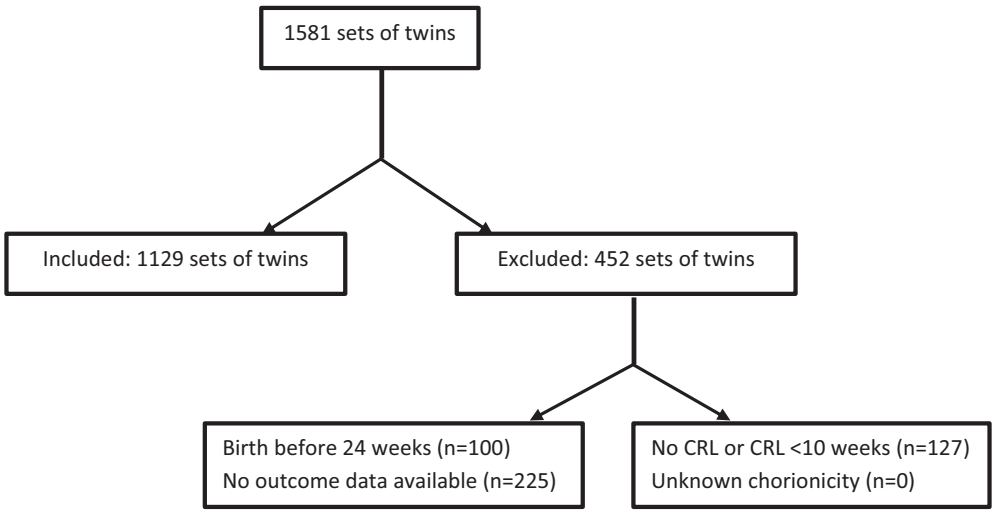

FIGURE 2 | Cohort inclusion and exclusion flowchart.

TABLE 1 | Maternal demographic and pregnancy characteristics for the 1129 mothers with twin pregnancies included in this study.

Variable	Value
Maternal age (years)	33.0 (33.0–36.0)
Maternal weight (kg)	66.9 (59.0–77.0)
Maternal height (cm)	165.1 (160.0–170.2)
BMI (kg/m^2)	24.4 (21.8–27.9)
Racial origin	
White	731 (64.7)
Black	157 (13.9)
South Asian	121 (10.7)
East Asian	23 (2.0)
Mixed	46 (4.1)
Smoker	16 (1.4)
Alcohol	32 (2.8)
Parity	
Nulliparous	377 (33.3)
Parous	489 (43.3)
Unknown	263 (23.3)
Method of conception	
Assisted conception	209 (18.5%)
Chorionicity	
Dichorionic	876 (77.6)
Monochorionic diamniotic	241 (21.3)
Monochorionic monoamniotic	12 (1.1)

Note: Values shown as median (IQR) and as number (%).

3.5 | Preterm Birth and Perinatal Mortality

Extreme pre-term birth < 28 weeks occurred in 2.6% ($n = 24$), 2.6% ($n = 24$) and 2.4% ($n = 22$) when pregnancy dating was based upon CRL-S, CRL-M and CRL-L, respectively ($p = > 0.999$ for CRL-M vs. CRL-S and $p = 0.765$ CRL-M vs. CRL-L). Perinatal mortality occurred in 15 (1.6%) pregnancies or 17 (0.9%) of fetuses/neonates, where 6 of the 15 pregnancies with losses had an EFW discordance > 15%. These numbers were too small for meaningful statistical analysis based on CRL dating policy.

4 | Discussion

4.1 | Main Findings

The main findings of this study are that, irrespective of whether the pregnancy is dated by CRL-M, CRL-L or CRL-S, there was no significant difference in rates of extreme preterm birth < 28 weeks, sensitivity of prenatal detection of SGA fetuses or prevalence of SGA neonates at birth. These findings do not support the expert opinion-based guideline recommendations for dating by CRL-L. In contrast, dating by CRL-M would reduce unnecessary stigmatisation of the smaller twin without compromising gestational age assessment or adverse pregnancy outcomes.

4.2 | Interpretation

4.2.1 | Twin Dating to Assess Gestational Age at Birth

The median inter-twin CRL discordance was 2 mm which is equivalent to a difference of 4% or 1.4 days. Consequently, dating by CRL-S, CRL-L or CRL-M had a minimal effect on gestation of birth, which varied by < ±1 day with any strategy. Most previous studies that looked at the direct impact of CRL differences estimated an average difference of between 1 and 3 days of gestation depending on whether the larger or smaller CRL measurement was used [5, 14–16, 22, 23].

Considering gestational age based upon artificial reproductive techniques (ART) such as in vitro fertilisation (IVF) in comparison to ultrasound-based gestational age, some suggest that the smaller twin CRL is closer to the gestation-specific CRL based upon ART [14, 15]. However, 'true' gestational age is unknown, and variation also exists when the assumed date of conception is calculated from the embryo transfer date whilst correcting for fresh/frozen cycles and blastocyst stage. Furthermore, conflicting data also exist about early pregnancy growth in IVF and naturally conceived fetuses, with IVF dating shown to systematically underestimate size and gestational age [16, 24, 25]. Dias et al. assessed a large cohort of singleton and twin IVF pregnancies dated by the embryo transfer date and demonstrated that IVF dating underestimated the gestational age in singleton pregnancies and that dating from twin CRL-M was the most approximate to singleton dating [16]. The latter findings support both dating by CRL in singleton IVF pregnancies and by CRL-M in twin IVF pregnancies. Suggested limitations of relying on CRL-S due to 'pathological' smallness are mitigated by a large systematic review demonstrating that a > 40% CRL discordance is required to increase the risk of adverse pregnancy outcome [26]. As in the current study, a very small proportion of pregnancies exhibited CRL discordances of > 25% and none > 40%, limiting the risk of adverse pregnancy outcome, again supporting dating by CRL-M [5, 26, 27].

4.3 | Small for Gestational Age Birth

There was no significant difference between various first trimester CRL dating strategies in rates of detection for fetuses with SGA < 10th centile or the rate of SGA birth < 10th centile. Assessment of fetal size and SGA diagnosis has been proposed as the most important reason for accurate pregnancy dating [16, 28]. The concern has always been that dating by the smaller twin will potentially reduce the detection of SGA fetuses, whilst dating by the larger twin may result in an inflated SGA rate. However, there are no published studies of the impact of various first trimester CRL dating approaches on the rates of SGA

TABLE 2 | Crown-rump length distributions, gestational ages at CRL or birth, preterm birth rate and EFW and BW distributions depending on dating being performed by CRL-S, CRL-M or CRL-L.

	Dating by CRL-S	Dating by CRL-M	Dating by CRL-L	*p*	*p*
11 to 14-week scan				CRL-S vs. CRL-M	CRL-M vs. CRL-L
CRL (mm)	61.0 (56.0–66.0)	62.0 (57.2–67.2)	63.1 (58.4–68.9)	**< 0.001**	**< 0.001**
CRL-based gestation (weeks)	12.5 (12.2–12.9)	12.6 (12.2–13.0)	12.7 (12.3–13.1)	**< 0.001**	**< 0.001**
Fetal well-being scan					
Smaller twin median EFW centile	33.7 (14.3–54.9)	31.2 (13.2–53.0)	29.5 (12.1–50.3)	0.074	0.084
Smaller twin EFW < 10th centile	19.8%	21.7%	23.1%	0.275	0.419
Smaller twin EFW < 3rd centile	10.1%	11.5%	12.2%	0.308	0.601
Larger twin median EFW centile	63.4 (43.3–79.2)	60.6 (41.1–77.2)	57.7 (37.8–74.9)	**0.021**	**0.024**
Birth					
Gestation (weeks)	36.5 (34.6–37.3)	36.6 (34.7–37.3)	36.6 (34.9–37.4)	0.179	0.173
Preterm birth (< 37 weeks)	64.4%	61.0%	58.9%	0.133	0.364
Extreme preterm birth (< 28 weeks)	2.6%	2.6%	2.4%	1.000	0.765
Smaller twin median BW centile	13.2 (5.2–28.1)	12.2 (4.6–26.5)	11.2 (4.2–25.2)	0.159	0.209
Smaller twin BW < 10th centile	43.6%	47.1%	49.5%	0.132	0.325
Smaller twin BW < 3rd centile	19.1%	20.5%	23.8%	0.445	0.091
Larger twin median BW centile	37.0 (20.6–56.9)	35.4 (18.9–54.4)	33.4 (18.1–53.4)	0.122	0.157

Note: Values are shown as median (IQR) and as proportion (%). Bold values indicates signifcance (*p*-values).
Abbreviations: BW, birthweight; CRL, Crown-rump length; CRL-L, CRL of larger twin; CRL-M, mean CRL measurement; CRL-S, CRL of smaller twin; EFW, estimated fetal weight.

detection or birth. Only one case–cohort study of 176 twin pregnancies suggested that SGA detection may be more accurate when dating by the smaller twin but that it resulted in a higher missed diagnosis rate [17].

Even though SGA detection is a standard part of antenatal care, there is little consensus on how to define SGA in twin fetuses. The use of growth charts for twin pregnancies is controversial as they may normalise pathological poor growth by using a retrospectively selected reference cohort [16, 29]. Inter-twin size and Doppler discordance appears more important than SGA of one or both twins in predicting pregnancy outcome [28, 30]. The Southwest Thames Obstetric Research Collaborative (STORK), in a large retrospective multi-centre cohort study, reported a progressive increase in the risk of neonatal morbidity with increasing birthweight discordance, regardless of a diagnosis of SGA in either twin [31]. Importantly, assessment of inter-twin size discordance can be calculated even without accurate gestational age assessment as it reports on the relative size of the twins, in contrast to SGA alone, which is gestationalage dependent.

4.4 | Adverse Pregnancy Outcomes of Preterm Birth and Perinatal Mortality

Various twin CRL dating policies also did not influence the extreme premature birth rate, and the perinatal mortality was too low to demonstrate any changes with different CRL dating approaches. Several studies have examined the relationship of inter-twin discordance on perinatal mortality, but none have evaluated the impact of CRL dating strategies on extreme preterm birth or perinatal mortality rates. The finding of this study is supported by the published evidence relating CRL

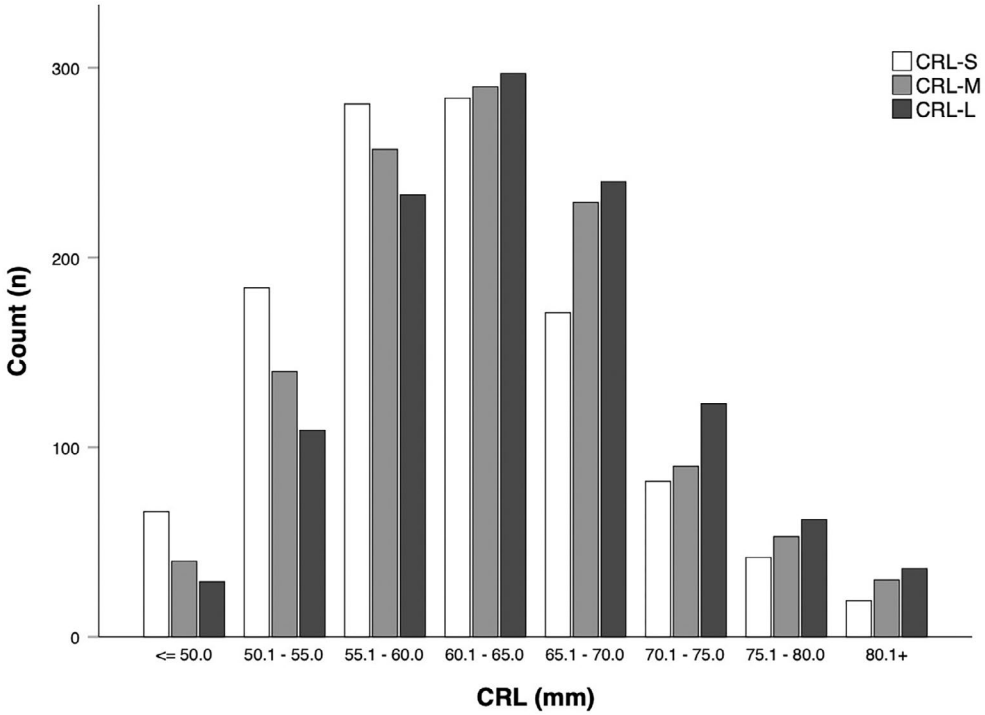

FIGURE 3 | Twin crown-rump length measurement distribution. Crown-rump length (mm) distribution based upon measurement of the smaller twin, mean twin measurement and the larger twin.

TABLE 3 | Screening performance of estimated fetal weight < 10th and < 3rd centiles for the prediction of small for gestational age birth < 10th and < 3rd centiles.

	Dating by CRL-S	Dating by CRL-M	Dating by CRL-L	*p**
SGA birth < 10th centile				
Sensitivity	37.8 (33.1–42.7)	38.4 (33.9–43.1)	39.4 (35.0–44.0)	0.351 (CRL-S vs. CRL-M)
Specificity	93.8 (91.5–95.6)	93.3 (90.9–95.3)	93.0 (90.5–95.1)	0.435 (CRL-M vs. CRL-L)
SGA birth < 3rd centile				
Sensitivity	29.7 (23.2–36.7)	31.9 (25.5–38.8)	30.2 (24.4–36.6)	0.431 (CRL-S vs. CRL-M)
Specificity	94.8 (93.1–96.3)	94.1 (92.2–95.6)	93.9 (92–95.6)	0.577 (CRL-M vs. CRL-L)

Abbreviations: CRL, Crown-rump length; CRL-L, CRL of larger twin; CRL-M, mean CRL measurement; CRL-S, CRL of smaller twin; SGA, small for gestational age.
*Univariate analysis for true positive cases. Sensitivity and specificity are expressed as percentages with 95% confidence intervals.

discordance to perinatal mortality which demonstrate that CRL discordance is associated with, but has poor predictive performance for adverse pregnancy outcome [5, 26, 27]. In a large systematic review, twin pregnancy CRL discordance of > 15% was associated with, but not significantly predictive of, perinatal loss until CRL discordance was greater than 40% [26]. In the current cohort, one of the 1129 twin pregnancies had an inter-twin CRL discordance of > 25%, explaining both the rarity of this finding and the minimal impact of dating by CRL on this parameter. In contrast to first trimester twin CRL discordance, inter-twin growth discordance in later pregnancy is recognised as an independent risk factor for adverse perinatal outcome and is associated with a substantial increase in preterm delivery, perinatal morbidity and mortality [22, 29, 31, 32]. These data question the value of setting a CRL discordance threshold below 40% in the first trimester as an indicator of subsequent fetal wellbeing.

4.5 | Clinical Implications

Based on the existing evidence, there is little doubt that CRL discordance is associated with an increase in risk for adverse outcome, but it remains a poor predictor when the CRL discordance is < 25% [26]. In contrast, dating by the smaller or bigger twin has a minimal effect on gestational age at birth, rates of extreme preterm birth, ultrasound detection of SGA foetuses or birth of SGA neonates. These findings are not consistent with the recommendations from international guidelines which routinely recommend the use of the larger twin CRL to date the pregnancy so as not to miss subsequent fetal growth restriction [6–10]. Whilst there is ample evidence that inter-twin CRL discordance is related to adverse pregnancy outcome, there is none to show that dating has a similar effect, thereby calling into question the rationale for dating by the larger twin. We have

demonstrated that dating by the mean twin CRL does not significantly change the gestational age at birth or SGA detection compared to dating by the larger and smaller twin. Furthermore, such a policy would remove the current systematic stigmatisation of the smaller twin which results from dating by the larger CRL and heightens parental anxiety associated with the effect of exaggerating the smaller twin's apparent lack of growth in early pregnancy (Figure 1). Doing so increases antenatal surveillance beyond that of routine 4-weekly growth assessment in dichorionic pregnancies for example.

A policy of dating by the mean twin CRL size does not preclude the calculation of twin CRL or EFW discordance, which are commonly used predictors of adverse pregnancy outcome, albeit of modest value.

4.6 | Strengths and Limitations

This is a large and well-curated twin dataset with relevant clinical outcomes such as gestation at birth, rates of extreme preterm birth, detection of SGA on ultrasound and rates of SGA at birth. A systematic and robust analysis of the impact of the three dating strategies on relevant clinical outcomes was conducted. However, this is a retrospective study where exclusion of births < 24 weeks and treatment paradox due to clinical interventions might have reduced perinatal mortality. A specific limitation is that within the study population, routine practice was to date the pregnancy based upon the larger twin CRL. This may have influenced management at the time and consequently the outcomes explored within this study. The scan-to-birth interval was not the same in all cases and may have affected SGA detection rates—but this should have been equally evident for all CRL dating strategies. None of these factors are likely to have influenced the analysis of various dating options, but a larger-scale multi-centre study would be required to determine impact on perinatal mortality. Finally, the assumption made during analysis that the smaller twin on ultrasound is the smaller twin at birth may have occasionally been incorrect, but this is unlikely to have had a significant impact on the measured outcomes.

5 | Conclusions

We present a statistical, biological and pathological argument for undertaking dating in twin pregnancies by the mean twin CRL in the first trimester. Dating by the smaller, larger or mean twin size does not significantly alter the prediction of gestational age, rates of extreme preterm birth, detection of SGA fetuses or rates of SGA birth. The modest differences in twin fetal size in the first trimester represent normal biological variability rather than an underlying pathological process. Dating by the mean twin CRL retains the utility of accurate gestational assessment without impacting clinical outcomes.

Author Contributions

G.V.B. and V.G. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. G.V.B. undertook manuscript writing. G.V.B. and V.G. completed table and figure preparation. A.B. and B.T. reviewed and edited the manuscript. All authors undertook revision and final approval of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.