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MATERNAL-FETAL MEDICINE

The value of ultrasound in predicting isolated inter-twin discordance and adverse perinatal outcomes

Xinning Chen[1] · Qiongjie Zhou[1,2,3] · Xirong Xiao[1] · Xiaotian Li[1,2,4]

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Abstract

Purpose To investigate the value of ultrasound approaching delivery to predict isolated inter-twin discordance and adverse perinatal outcomes.

Methods We retrospectively included twin pregnancies with sonography approaching delivery in ten maternal–foetal medicine centres in China from 2013 to 2014. Estimated foetal weight (EFW) and inter-twin EFW disparity (EFWD) were calculated based on biometry parameters. Percentage errors between EFW and actual birthweight or between EFWD and actual inter-twin disparity were calculated. ROC curves and multiple logistic regression were applied to evaluate the ability of EFWD to predict inter-twin disparity ≥ 25%, stillbirth, asphyxia and admission to a neonatal intensive unit (NICU). Chorionicity-stratified analysis was further performed.

Results Two hundred sixty-six monochorionic and 760 dichorionic twin pregnancies were analysed. The percentage errors in foetal weight estimations were 7–13%, whereas percentage errors in the estimation of inter-twin disparity were nearly 100%. Among eight formulas, Hadlock1 performed best, with a detectable rate of 65% and a false positive rate of 5% when predicting inter-twin disparity ≥ 25%. EFWD ≥ 22% was strongly associated with stillbirth (OR = 4.17, 95% CI 1.40–12.40) and NICU admission (OR = 3.48, 95% CI 2.03–5.97) after adjustment for gestational age, parity and abnormal umbilical systolic/diastolic ratio. Ultrasound had better predictive ability in monochorionic twins.

Conclusion The predictive value of ultrasound for isolated inter-twin discordance and adverse perinatal outcomes was limited, which was possibly due to the magnifying of systematic errors in the disparity estimation compared with weight estimation. Despite this, abnormal biometry was an independent contributor for the poor prognosis of neonates.

Keywords Inter-twin discordance · Ultrasound · Estimated fetal weight (EFW) · Stillbirth · Admission to neonatal intensive care unit

Introduction

Although inter-twin discordance of birth weights is inevitable, inter-twin discordance greater than a certain value is associated with enhanced morbidity and mortality both for neonates and mothers [1–5]. Furthermore, isolated inter-twin discordance, which excludes other complications leading to inter-twin discordance such as twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion sequence (TRAP), twin anaemia polycythaemia sequence (TAPS), foetal anomalies or intrauterine death, is also related to adverse perinatal outcomes [4]. Therefore, it is of great value and clinical significance to identify isolated inter-twin discordance and furthermore to predict the prognosis before delivery.

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✉ Xiaotian Li
xiaotianli555@163.com

1 Obstetrics and Gynecology Hospital, Fudan University, 419 Fangxie Road, Shanghai 200011, China

2 Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Shanghai, China

3 Women's Health and Perinatology Research Group, Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway

4 Institute of Biomedical Sciences, Fudan University, Shanghai, China

Ultrasound before delivery is a widely accepted method to detect inter-twin discordance. Previous studies reported that the disparity in biometry parameters such as crown–rump-length (CRL), abdominal circumstances (AC) or estimated foetal weight (EFW) are associated with perinatal loss and preterm birth [6–11]. The Doppler indices of middle cerebral or umbilical artery were also valuable references for selective foetal restriction and placenta insufficiency [12, 13]. However, the accuracy of sonography in predicting inter-twin discordance and adverse outcomes remains inconclusive [14–21] because it may be affected by different formulas, cut-offs, gestational ages of examination or chorionicity. The formulas of estimated foetal weight based on sonographic parameters are mainly derived from singletons, resulting in lower accuracy in twin gestations because of different growth patterns [22–24]. Meanwhile, the distinct pathophysiology of mono- and dichorionic twins triggers inconsistent development patterns [25]. It is still unclear whether ultrasound itself is a satisfying predictive tool when controlling for these affecting factors.

The primary aim of our study was to evaluate the ability of ultrasound to predict isolated inter-twin disparity ≥ 25% and adverse perinatal outcomes, including stillbirth, neonatal asphyxia and admission to neonatal intensive care unit (NICU). The second aim was to compare the accuracy of ultrasound in mono- and dichorionic twins.

Materials and methods

Study population

This study was a part of the large multi-centred cohort study in China that collected antenatal and perinatal information from 3246 twin gestations registered at ten maternal–foetal medicine centres from 2013 to 2014 by the Collaborative Group on Twin Birth and Foetal Abnormality in China (CGTBFA) (full details were provided in the previous published paper [26]). Our study retrospectively collected pregnancies that had available sonography records within 7 days of delivery from the database. The inclusion criteria involved the following: (1) having routine antenatal examination in these hospitals; (2) maternal age 18–50 years old; (3) gestational age (GA) at delivery ≥ 28 weeks (perinatal period was defined as 28 weeks GA to 7 postnatal days in China [23]); and (4) availability of ultrasound parameters within 7 days of delivery (only the latest one was adopted if there were more than one sonography). The exclusion criteria included the following: (1) inability to determine chorionicity or monoamniotic twin pregnancies; (2) pregnancies with major structural or chromosomal disorders; (3) TTTS, TRAP, or TAPS confirmed before last ultrasound; and (4) intrauterine foetal death confirmed before last ultrasound. The exclusion criteria were strictly set to control the bias of other complications in twin gestations that resulted in birth weight discordance. Cases missing important value, such as birth weight, were excluded as well. Informed consent was obtained from all participants included in the study. This study obtained ethical approval from each institutional ethics committee of the 10 collaborating hospitals (Obstetrics and Gynecology Hospital of Fudan University, First Affiliated Hospital of Sun Yat-sen University, First Affiliated Hospital of Chongqing Medical University, Gulou Clinical Medical College of Nanjing Medical University, Peking University First Hospital, Shandong Provincial Hospital of Shandong University, Shanghai First Maternity and Infant Health Institute Affiliated with Tongji University, Shengjing Hospital of China Medical University, Third Hospital Affiliated with GuangZhou Medical University, and Women's Hospital School of Medicine at Zhejiang University).

Data collection

Gestational age was determined by last menstrual period and confirmed by the CRL of the larger foetus at 11–14 weeks [27–29]. If the difference between the two methods was greater than 7 days, then the result according to CRL was treated as the more accurate estimate. Before 10 weeks' gestation, chorionicity was determined by ultrasound through the number of gestational sacs, amniotic sacs and yolk sacs, while it was determined by the number of placentas, identification of peak signs and membrane characteristics after 10 weeks [30, 31]. The chorionicity was finally confirmed after delivery.

Ultrasound scans were performed by different ultrasound physicians in tertiary hospitals in China utilizing the same type of machines (3.5–5 MHz curvilinear abdominal transducer). To minimize the measurement bias, ultrasonographers accepted regular and unified training. We performed quality control of the images 4 times a year randomly [32]. The biometry parameters included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral length (FL). Estimated foetal weight (EFW) was calculated using the Hadlock 1, 2, 3, 4 formula [33, 34] and the Ong [35], Ott [36], Shepard [37], and Combs [38] formulas. Additionally, the umbilical artery systolic/diastolic (S/D) ratio was obtained from pulsed Doppler examination and calculated using peak systolic velocity/end-diastolic velocity. An S/D ratio of either foetus in pairs ≥ 90th‰ was classified as abnormal. If intermittently or persistently absent/reversed end-diastolic flow was observed, the Doppler indices were also classified as abnormal, irrespective of the S/D ratio [39, 40]. The reference percentile of the umbilical S/D ratio dependent on gestational age was derived from previous studies [41].

The primary outcome of this study was actual birth weight disparity (actual BWD) ≥ 25%, as several large and well-designed studies demonstrated the substantially increased risk of poor prognosis at this cut-off [42–46]. BWD was calculated as 100% × (birth weight of larger infant – birth weight of smaller infant)/birth weight of larger infant, and weight data were obtained from medical records. The secondary outcomes involved stillbirth, neonatal asphyxia, and admission to NICU (neonatal intensive care unit). Stillbirth was defined as a baby born without signs of life after 28 weeks of gestation. Neonatal asphyxia was defined as the inability of a foetus to establish an effective spontaneous breathing with 1-min-Apgar score ≤ 7 or 1-min-Apgar score > 7 but deteriorating to ≤ 7 at 5 min after birth [47].

Potential confounders were collected from the first antenatal visit and medical records of the new-borns. These involved maternal age, maternal BMI at first antenatal visit, parity, history of abnormal pregnancy, use of assisted reproductive technology (ART), chorionicity, abnormal S/D ratio and gestational age at delivery.

Analysis and statistics

EFW disparity (EFWD) was calculated as 100% × (larger EFW − smaller EFW)/larger EFW. Two types of errors were calculated and analysed. To assess the errors between EFW and actual weight, the percentage error of EFW was calculated as 100% × (actual BW − EFW)/actual birth weight, whereas the absolute percentage error of EFW was calculated as 100% × |actual BW − EFW|/actual BW. To investigate the errors between sonographic EFW disparity and actual BW disparity, the percentage error of EFWD was 100% × (BWD − EFWD)/BWD, while the absolute percentage error of EFWD was 100% × |BWD − EFWD|/BWD. Statistical tests included the Kolmogorov–Smirnov test, Levene's test and Student's *t* test for paired samples and were carried out to compare absolute percentage errors. In addition, reliability analysis was calculated using Cronbach's alpha value to evaluate the consistency of EFW and actual BW, as well as EFWD and BWD ($\alpha \geq 0.9$ excellent correlation, $\alpha < 0.5$ unacceptable correlation) [48].

ROC curves were constructed; meanwhile, positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were established to evaluate the predictability of EFWD. Moreover, univariable and multivariable logistic regressions were performed to explain the association between EFWD and adverse outcomes. In all regression analyses, we adjusted for the same covariates (abnormal umbilical S/D ratio, gestational age at delivery, parity) for the basic model because they were statistically significantly associated with adverse perinatal outcomes in the univariable regression. In further adjusted models, which may lead to over-adjustment, additional potential confounders were added (maternal age, maternal BMI, history of abnormal pregnancy, use of assisted reproductive technology and chorionicity) because all had a previous reported association with the outcomes [49–53]. The missing data represented less than 10% for all included covariates, except S/D ratio, which was associated with 11.2% missing data.

We performed a further stratified analysis based on chorionicity. The percentage errors, Cronbach's alpha, and area under the ROC curves in mono- and dichorionic twins were compared. The predictability of EFWD for adverse perinatal outcomes was also analysed separately in the mono- and dichorionic subgroups.

All data and calculations were stored and performed using SPSS version 22.0 (Chicago, IL, USA). Statistical significance was set at $P < 0.05$, and all P-values were two-tailed.

Results

A total of 1026 twin gestations were analysed (Fig. 1, study profile), comprising 266 monochorionic twins and 860 dichorionic twins. Out of all the potential parameters in sonography, 98.8% were eligible for BPD measurement, 97.7% for HC, 99.4% for AC and 99.3% for FL. Compared with analysed participants, excluded gestations that lacked last ultrasound were more likely to be monochorionic twins and were less likely to use artificial reproductive technology (Suppl 1). Otherwise, no significant differences in characteristics were observed.

Table 1 presents the baseline characteristics of all participants and the different characteristics of the mono- and dichorionic twin gestations. The mean maternal age of the participants was 29.9 (29.90 ± 5.06) years. The median GA

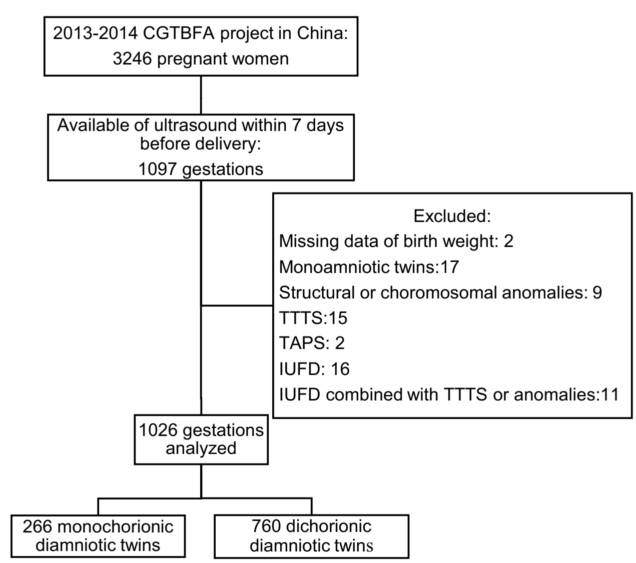

Fig. 1 Study profile

Table 1 Comparison of baseline characteristics between mono and dichorionic twins

	Overall	Monochorionic	Dichorionic	*P* value[b]
N	1026	266	760	
Maternal age (years)	29.90 ± 5.06	28.71 ± 4.28	30.31 ± 5.24	< 0.000
Maternal BMI (kg/m^2)	21.35 ± 2.94	21.16 ± 2.70	21.42 ± 3.01	0.217
Nulliparous	833 (81.2%)	209 (78.6%)	624 (82.1%)	0.204
History of abnormal pregnancy[a]	46 (4.5%)	9 (3.4%)	37 (4.9%)	0.314
Use of assisted reproductive technology	529 (51.6%)	46 (17.3%)	483 (63.6%)	< 0.000
GA at delivery (weeks)	35.12 ± 2.17	34.94 ± 2.26	35.66 ± 2.16	< 0.000
BW of smaller fetus (g)	2184.21 ± 502.57	2001.13 ± 506.58	2248.28 ± 485.43	< 0.000
BW of larger fetus (g)	2458.92 ± 495.86	2299.98 ± 469.14	2514.55 ± 493.21	< 0.000
Actual birth weight disparity (%)	11.41 ± 9.76	13.39 ± 11.29	10.72 ± 9.07	0.001
Inter-twin discordance	91 (8.9%)	41 (15.4%)	50 (6.6%)	< 0.000
Neonatal Asphyxia	84 (8.2%)	21 (7.9%)	63 (8.3%)	0.840
Stillbirth	24 (2.3%)	13 (4.9%)	11 (1.4%)	0.001
NICU admission	386 (37.6%)	117 (44.0%)	269 (35.4%)	0.013
Missing information of				
BPD parameter	12 (1.2%)	3 (1.1%)	9 (1.2%)	> 0.999
HC parameter	24 (2.3%)	3 (1.1%)	21 (2.8%)	0.199
AC parameter	6 (0.6%)	3 (1.1%)	3 (0.4%)	0.378
FL parameter	7 (0.7%)	2 (0.8%)	5 (0.7%)	> 0.999
Umbilical S/D ratio	115 (11.2%)	24 (9.0%)	91 (12.0%)	0.189

[a]History of abnormal pregnancy included recurrent spontaneous abortion, intrauterine fetal death, embryo damage (GA ≥ 14 weeks), ectopic pregnancy and fetal anomalies

[b]The mean differences between the mono and dichorionic twins were compared by independent test, and proportions were compared by Chi square test

at delivery was 36 + 1 weeks (range 28 + 1 to 40 + 2 weeks), whereas monochorionic twins had a shorter gestational duration (median 35 + 4 weeks vs 36 + 3 weeks). The monochorionic twins exhibited a higher birthweight disparity than the dichorionic twins ($P = 0.001$). The general prevalence of stillbirth, neonatal asphyxia and NICU admission was 2.3% (24/1026), 8.2% (84/1026), and 37.6% (386/1026), respectively, and monochorionic twins suffered from a higher incidence for all complications except asphyxia. Suppl 2 presents the regional differences. Participants in Beijing had higher BMI values than average. Participants in Guangzhou were more likely to be multiparous, with a higher proportion of ART use. The prevalence of monochorionic twins, neonatal asphyxia and NICU admission varied greatly across cities, which was associated with diversity in gestational age at delivery, reflecting the higher rate of preterm birth in monochorionic twins and the potential interaction between these variations.

Table 2 summarizes the median percentage error, the mean absolute percentage error and Cronbach's values of eight EFW formulas. Median percentage errors in the weight estimation of the larger foetus as well as median percentage errors in the estimation of disparity were all positive numbers, with the exception of the Shepard formula. Thus, the true weight of the larger foetus and BWD are more likely to be under-estimated by ultrasound, whereas the true weight of the smaller foetus may be over-estimated or under-estimated. The mean absolute percentage errors in the weight estimation of the smaller foetus (range 8.42–13.11%) were higher than those concerning the larger foetus (range 7.69–12.36%) ($P < 0.05$) according to all eight studied formulas, which indicated that the weight estimation of the lager foetus was more accurate. The mean absolute percentage errors in disparity estimation were over 95% based on all formulas. Reliability analysis reveals that EFWs in all formulas were perfectly correlated with the actual birth weights (Cronbach's value > 0.9), whereas EFWD and actual BWD exhibited a correlation but were not perfect (Cronbach's value range 0.669–0.761). Among the 8 formulas, Hadlock1 and Hadlock3 performed better, with lower mean absolute percentage errors and higher Cronbach's alpha. Further chorionicity-stratified analysis in Suppl 3 demonstrates that the estimation of disparity in monochorionic twins is more accurate, with lower mean absolute percentage errors and higher Cronbach's alpha, thanks to the more precise estimation of the larger foetus.

Table 3 shows the screening of actual birth weight disparity ≥ 25% using EFWD based on different formulas. The

Table 2 The Median percentage error, mean absolute percentage error, Cronbach's value of eight formulas

	Weight estimation of smaller fetus	Weight estimation of larger fetus	Estimation of inter-twin disparity
Median percentage error[a] (%)			
Hadlock1	1.31 (−52.03 ~ 38.59)	2.51 (−43.30 ~ 56.38)	14.17 (−3152.97 ~ 100.00)
Hadlock2	1.55 (−52.04 ~ 37.26)	3.32 (−41.85 ~ 35.93)	19.62 (−4523.13 ~ 100.00)
Hadlock3	0.51 (−50.51 ~ 36.98)	1.47 (−46.49 ~ 55.47)	12.27 (−4693.72 ~ 100.00)
Hadlock4	2.28 (−54.92 ~ 39.07)	3.45 (−39.69 ~ 37.54)	15.79 (−3209.49 ~ 99.94)
Ong	0.33 (−57.16 ~ 42.54)	2.54 (−44.58 ~ 38.12)	24.93 (−3158.06 ~ 100.00)
Ott	−1.97 (−69.39 ~ 42.33)	0.47 (−44.07 ~ 35.49)	19.10 (−3577.80 ~ 100.00)
Combs	−1.78 (−71.47 ~ 35.51)	0.98 (−42.78 ~ 35.27)	22.51 (−3135.29 ~ 100.00)
Shepard	−8.48 (−67.44 ~ 38.53)	−8.25 (−72.56 ~ 31.17)	−3.62 (−6028.03 ~ 100.00)
Mean absolute percentage error[b] (%)			
Hadlock1	8.42 ± 7.39	7.69 ± 6.56*	101.19 ± 220.97
Hadlock2	8.70 ± 7.59	8.19 ± 6.86*	113.28 ± 278.81
Hadlock3	8.39 ± 7.39	7.69 ± 6.48*	107.21 ± 265.39
Hadlock4	8.72 ± 7.53	8.07 ± 6.88*	102.41 ± 227.71
Ong	8.74 ± 7.90	8.10 ± 6.78*	108.78 ± 245.29
Ott	9.31 ± 8.42	7.94 ± 6.87*	99.92 ± 231.64
Combs	9.38 ± 8.70	7.92 ± 6.86*	95.65 ± 212.33
Shepard	13.11 ± 10.88	12.36 ± 9.45*	143.54 ± 358.89
Cronbach's alpha[c]			
Hadlock1	0.938 (0.930 ~ 0.945)	0.930 (0.921 ~ 0.938)	0.761 (0.729 ~ 0.789)
Hadlock2	0.935 (0.927 ~ 0.943)	0.925 (0.915 ~ 0.934)	0.704 (0.665 ~ 0.738)
Hadlock3	0.940 (0.932 ~ 0.947)	0.930 (0.921 ~ 0.938)	0.731 (0.696 ~ 0.762)
Hadlock4	0.934 (0.925 ~ 0.942)	0.929 (0.920 ~ 0.937)	0.752 (0.719 ~ 0.781)
Ong	0.934 (0.925 ~ 0.941)	0.923 (0.913 ~ 0.932)	0.718 (0.681 ~ 0.750)
Ott	0.926 (0.917 ~ 0.935)	0.922 (0.912 ~ 0.931)	0.743 (0.709 ~ 0.773)
Combs	0.924 (0.914 ~ 0.933)	0.919 (0.909 ~ 0.929)	0.743 (0.709 ~ 0.773)
Shepard	0.915 (0.903 ~ 0.925)	0.910 (0.898 ~ 0.920)	0.669 (0.626 ~ 0.708)

*There was significant difference ($P < 0.05$) when comparing absolute percentage errors between weight estimation of smaller fetus and larger fetus using paired- *t* test

[a]Percentage error in weight estimation of larger/smaller fetus = (actual birth weight − EFW)/actual birth weight; percentage error in estimation of inter-twin disparity = (BWD − EFWD)/BWD. Median percentage error was presented as Median (the minimum ~ the maximum)

[b]Absolute percentage error in weight estimation of larger/smaller fetus = |actual birth weight − EFW|/actual birth weight; absolute percentage error in estimation of inter-twin disparity = |BWD − EFWD|/BWD. Mean absolute percentage error was presented as mean ± standard deviation

[c]Cronbach's value: inter-class reliability was calculated between actual BW and EFW or between BWD and EFWD

Table 3 The prediction of inter-twin discordance using different EFW formulas with ROC

	AUC (95% CI)	Cut-off[a] (%)	Sen	Spe	PPV	NPV
Hadlock1	0.884 (0.841–0.927)	22	0.65	0.95	0.53	0.97
Hadlock2	0.863 (0.816–0.910)	22	0.60	0.95	0.53	0.96
Hadlock3	0.884 (0.842–0.926)	22	0.61	0.95	0.53	0.96
Hadlock4	0.877 (0.834–0.920)	22	0.61	0.95	0.54	0.96
Ong	0.877 (0.835–0.920)	22	0.59	0.95	0.55	0.96
Ott	0.875 (0.832–0.918)	20	0.57	0.95	0.50	0.96
Combs	0.874 (0.831–0.917)	19	0.58	0.95	0.52	0.96
Shepard	0.849 (0.803–0.895)	26	0.46	0.95	0.46	0.95

Sen sensitivity, *Spe* Specificity, *PPV* positive predictive value, *NPV* negative predictive value

[a]Cut-offs were adopted in order to control specificity at 0.95

areas under the ROC (AUC) range from 0.849 to 0.884. When false positive rates were all controlled at 5%, the cut-off points of EFWD were from 19 to 26%, and the detection rates varied from 0.46 to 0.65. EFWD exhibited superior performance in monochorionic twins with higher AUC (Suppl 3).

We then assessed the role of EFWD in predicting other adverse perinatal outcomes (Table 4). We adopted Hadlock1 formula and the threshold of 22% due to its better performance according to results described above. EFWD ≥ 22% exhibited low sensitivity but rather high specificity in identifying perinatal outcomes. The risk of stillbirth for twins with EFWD ≥ 22% was 4.166 (95% CI 1.400–12.400), whereas the risk of NICU admission was 3.477 (95% CI 2.026–5.966) after adjusting for abnormal S/D ratio, parity and GA at delivery in the basic model. Subgroup analysis illustrated that EFWD ≥ 22% was correlated with all adverse outcomes in monochorionic twins but associated only with NICU admission in dichorionic twins ($P < 0.000$).

Discussion

Main findings

Our study was a multi-centred design in China with a large sample size and few missing data. Our findings demonstrated that the existing EFW formula was not satisfactory for twins, and the Hadlock1 formula was relatively more accurate. The predictive value of EFW disparity was moderate for actual birthweight disparity ≥ 25%, as its detection rate was approximately 60% when the false positive rate was 5%. Despite this, EFW disparity was indeed an independent predictor of stillbirth and NICU admission. EFW disparity exhibited better performance in monochorionic twins.

The rigorously set exclusion criteria made our study robust. We excluded unique complications for monochorionic twins, including TTTS, TAPS and TRAP, which primarily resulted from unbalanced vascular anastomoses [54–56] and eventually led to inter-twin discordance. Selective intrauterine growth restriction (sIUGR), on the other hand, was defined as EFW of the smaller foetus below the 10th‰ and an EFWD ≥ 25% [57]. Instead of shared circulation such as TTTS, unequal placenta sharing played an indispensable role in the pathophysiology of both sIUGR and

Table 4 Overall and stratified analysis of prediction accuracy and odds ratio (OR) for the risk of adverse perinatal outcomes with EFWD ≥ 22%

	Sensitivity% (95% CI)	Specificity% (95% CI)	Crude OR	*P* value	Basic aOR[a]	*P* value	Fully aOR[b]	*P* value
Overall analysis								
Stillbirth	27.27 (10.73–50.22)	89.92 (87.85–91.74)	3.344 (1.279–8.745)	0.014	4.166 (1.400–12.400)	0.010	3.766 (1.198–11.834)	0.023
Neonatal Asphyxia	18.75 (10.89–29.03)	90.26 (88.15–92.11)	2.139 (1.171–3.908)	0.013	1.889 (0.914–3.901)	0.086	2.026 (0.922–4.452)	0.079
Admission to NICU	18.55 (14.73–22.88)	94.37 (92.26–96.05)	3.819 (2.485–5.869)	< 0.000	3.477 (2.026–5.966)	< 0.000	3.244 (1.820–5.783)	< 0.000
In monochorionic twins								
Stillbirth	45.45 (16.75–76.62)	86.59 (81.85–90.48)	5.381 (1.559–18.577)	0.008	7.413 (1.738–31.618)	0.007	10.125 (2.102–48.770)	0.004
Neonatal Asphyxia	33.33 (14.59–56.97)	86.85 (82.03–90.77)	3.303 (1.242–8.786)	0.017	2.882 (0.943–8.803)	0.063	5.337 (1.449–19.658)	0.012
Admission to NICU	22.22 (15.06–30.84)	90.97 (85.31–94.97)	2.878 (1.427–5.801)	0.003	2.650 (1.114–6.306)	0.028	2.867 (1.132–7.261)	0.026
In dichorionic twins								
Stillbirth	9.09 (0.23–41.28)	91.14 (88.81–93.12)	1.029 (0.130–8.166)	0.979	0.910 (0.096–8.596)	0.934	1.218 (0.115–12.844)	0.870
Neonatal Asphyxia	13.56 (6.04–24.98)	91.55 (89.17–93.56)	1.700 (0.769–3.761)	0.190	1.380 (0.504–3.779)	0.531	1.326 (0.439–4.008)	0.617
Admission to NICU	16.86 (12.48–22.03)	95.50 (93.21–97.20)	4.308 (2.493–7.443)	< 0.000	4.402 (2.138–9.063)	< 0.000	3.879 (1.763–8.534)	0.001

[a]OR adjusted for abnormal S/D ratio, GA at delivery and parity

[b]OR adjusted for abnormal S/D ratio, GA at delivery, parity, chorionicity, maternal age, maternal BMI at first visit, history of adverse pregnancy and use of assisted reproduction technology. In further chorionicity-stratified study, chorionicity was not included

inter-twin disparity [58]. There was a great overlap between inter-twin discordance and sIUGR. Therefore, we did not exclude cases of sIUGR but adopted the typical Doppler wave pattern of sIGUR (AREDF) as a confounding variable. Another strength of our study was the intuitive presentation of percentage errors. We revealed the magnifying trend of systematic errors in disparity estimation compared with weight estimation. We took a further step to compare the fitting accuracy of EFW formulas and predictive ability of ultrasound in mono- and dichorionic twins.

Our study had several limitations. First and foremost, admission bias was inevitable; the 10 centres in our study were all tertiary hospitals, where cases were relatively severe, leading to overestimated prevalence of complications. Second, selection bias emerged when we included only cases with ultrasound approaching delivery. Participants under frequent ultrasounds or pregnancies with potential complications were more likely to be enrolled. Despite this, we excluded pregnancies with complications as much as possible. Therefore, this is unlikely to change the findings significantly. Fourth, the Doppler indices were limited. We failed to obtain Doppler indices of the middle cerebral artery, as it was not a routine test. The missing data of umbilical S/D ratio accounted for 11.2% (115/1026). Fortunately, the proportion of missing Doppler data was balanced between chorionicity (Table 1), which implied random loss. Finally, it was a challenge to label the foetus in the ultrasound examination and match it with the newborn. We differentiated the larger foetus and the smaller foetus according to EFW and matched the larger foetus with the heavier infant upon delivery. However, concerns were raised when the EFWs of the two foetuses were similar, as there was error in weight estimation.

Interpretation of findings

In spite of abundant previous studies, the value of EFWD in predicting inter-twin birth weight discordance did not reach an agreement. Our findings resembled those in the study by Van de Waarsenburg et al. [16], which also focused on the last ultrasound and presented a sensitivity of 57% and a specificity of 94%. Khalil et al. [59] and Hoopmann et al. [60] obtained a similar sensitivity of approximately 0.65 and a specificity of approximately 0.9. The accuracy of prediction was probably influenced by different cut-offs, formulas and gestational ages. Our cut-off point of EFWD was slightly lower than the threshold of actual BWD. This was because the birth weight of the larger foetus was often underestimated, which was consistent with work by Reberdao et al. [61]. Eight different formulas were applied and compared with each other in our study. Compared with the Ong formula, which was designed specifically for twins, Hadlock1 performed better, with lower errors and higher sensitivity. Similarly, Esinler et al. [62] and Khalil et al. [59] suggested that formulas considering a combination of head, abdomen and femur measurements are better. Additionally, several studies demonstrated that the prediction was more accurate when the ultrasound was approaching delivery [16, 17, 63]. In our study, the average interval between ultrasound and labour was 2.53 ± 2.25 days. Thus, the errors in our study were primarily from ultrasound itself.

The calculation of EFWD introduced significant uncertainty in the ultrasound assessment. EFWD could be transformed to 1- (EFW of smaller one/EFW of larger one). If there were errors in both the numerator and denominator, the step of division would translate the smaller error into overwhelming deviation. The percentage errors between EFW and the BW were approximately 10% for either foetus, which was still within acceptable range. Supposing that the actual birth weights of a twin-pair were 2500 g and 2000 g, respectively, and the BW of the larger foetus was underestimated by 10%, as our results showed (EFW = 2250 g), whereas the BW of the smaller foetus was overestimated by 10% (EFW = 2200 g), the EFWD (2%) was just one-tenth of the actual BWD (20%). Therefore, this magnifying effect of errors was inevitable because it was derived from the calculation itself. Further studies about improved EFW formulas, utilization of MRI [64] or other advanced biomarkers should be explored to diminish the initial error.

Regardless of the low sensitivity when predicting adverse perinatal outcomes, our study demonstrated that twins with EFWD ≥ 22% had over three-fold higher risk of being stillborn or admitted to the NICU, even after adjustment. It was noteworthy that an abnormal S/D ratio was associated with adverse perinatal outcomes in light of our univariate regression. Several investigators have advocated for the role of Doppler indices in predicting growth restriction and inter-twin discordance [65, 66]. More recent work by Khalil et al. [21] also suggested that the umbilical artery pulsatility index (UA-PI) is an independent contributor for perinatal loss when converted into multiples of the median (MoM). Nevertheless, the abnormal S/D ratio in our study may not represent long-term impairment, as we included only the last ultrasound. The results should be interpreted with caution.

The different predictability of sonographic biometry was observed in mono- and dichorionic twins. Queiros et al. [67] also noted a higher sensitivity and specificity for inter-twin discordance in monochorionic pairs. The plausible reason seemed to be the better fitting of the larger foetus's weight in monochorionic twins. Whether this was due to the appropriate position was unknown. Discordance in monochorionic twins had a stronger association with poor prognosis, regardless of excluding specific complications for monochorionic twins. This result hinted that discordance was not a consequence of TTTS, TRAP or TAPS but was an independent complication in monochorionic twins. Regular monitoring by ultrasound was beneficial for monochorionic twins.

Conclusions

In conclusion, ultrasound examination had moderate predictive value for inter-twin discordance. The inevitable errors in the estimation of weight and disparity resulted in the limited detection rate. However, it was undeniable that abnormal biometry was an independent contributor for poor prognosis, especially in monochorionic twins, which influences decision-making and further management.

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Author contribution XC: data collection, data analysis, manuscript writing. QZ: data collection, manuscript editing. XX: data management, manuscript editing. XL: project development, funding acquisition, data management, manuscript editing.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval This study obtained ethical approval from each institutional ethics committee of 10 collaborative hospitals (Obstetrics and Gynecology Hospital of Fudan University, First Affiliated Hospital of Sun Yat-sen University, First Affiliated Hospital of Chongqing Medical University, Gulou Clinical Medical College of Nanjing Medical University, Peking University First Hospital, Shandong Provincial Hospital of Shandong University, Shanghai First Maternity and Infant Health Institute Affiliated with Tongji University, Shengjing Hospital of China Medical University, Third Hospital Affiliated with Guang-Zhou Medical University, and Women's Hospital School of Medicine at Zhejiang University). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

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