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Crown–Rump Length Discordance, Increased Nuchal Translucency, and Detection of Fetal Structural Anomalies in Twin Pregnancies in the First Trimester: 5 Years of Experience in a Tertiary Hospital in China

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Abbreviations

AUC, area under the receiving operator characteristic curveCRL, crown–rump length; DC, dichorionic; MC, monochorionic; MCDA, monochorionic-diamniotic; MCMA, monochorionic-monoamniotic; NT, nuchal translucency; OR, odds ratio; TRAPS, reversed arterial perfusion sequence; TTTS, twin-to-twin transfusion syndrome

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Objective—To evaluate the efficacy of the first-trimester ultrasound scan in the detection of fetal structural anomalies in twin pregnancies. To examine the association between increased nuchal translucency (NT) thickness, crown–rump length (CRL) or NT discordance, and detection of structural anomalies in a large twin series in China.

Methods—We performed retrospective analysis of twin pregnancies who underwent 11–13^{+6}-week and second-trimester anomaly scan and booked at Beijing Obstetrics and Gynecology Hospital between January 2012 and December 2016. Measurement of fetal CRL/NT and assessment of fetal anatomic structures were based on standard (not detailed) protocols. Conjoined twins and twin-reversed arterial perfusion sequence (TRAPS) were excluded from structural anomalies. The diagnostic performance of first-trimester ultrasound in detection of fetal structural anomalies in twins was determined and compared with that of second trimester. The accuracy of independent variates associated with structural anomaly detection was calculated.

Results—A total of 1442 women with twin pregnancies were included. In 40 women and 45 fetuses, structural anomalies were found. Fetal structural anomalies verified at delivery were detected in 42.5% (17/40) of affected pregnancies in the first trimester and 92.5% (37/40) of affected pregnancies in the second trimester ($P = .13$). The survival rate of pregnancies detected in second trimester was higher than that of pregnancies detected in first trimester (11.8% vs 65.2%). The mean value of intertwin CRL/NT discordance in cases with fetal structural anomalies was larger in monochorionic twins than dichorionic twins, but monochorionicity was not associated with structural anomalies. CRL discordance ≥10% (OR 3.1, 95%CI 1.5–6.3) and NT ≥95th centile (OR 20.0, 95%CI 9.0–44.2) were associated with fetal structural anomalies. In both dichorionic (DC) and monochorionic (MC) twins, the percentages of CRL discordance ≥10% was larger in twins with structural anomalies than those without structural anomalies (37.5% vs 13.4% in DC twins and 50.0% vs 12.5% in MC twins), and this was also true for NT ≥95th centile (31.3% vs 1.7% in DC twins and 37.5% vs 2.2% in MC twins). In the setting of CRL discordance ≥10% ， 40% (16/40) of twins with structural anomalies were found, in which the predominant fetal

structural anomalies were cardiovascular defects, abdominal wall defects, and central nervous system defects. The AUC for detecting structural anomalies by CRL discordance ≥10% was 0.63. In the setting of NT ≥95th centile ，32.5% (13/40) of twins with structural anomalies were found, in which the predominant fetal structural anomalies were cardiovascular defects, cystic hygroma, and abdominal wall defects. The AUC for detecting structural anomalies by CRL discordance ≥10% was 0.65.

Conclusions—The detection rate of twins with fetal structural anomalies was 42.5% per pregnancy in the first trimester. CRL discordance ≥10% and NT ≥95th centile may indicate higher risk of fetal structural anomalies in twins, but their efficacy was limited.

Key Words—fetal structural anomalies; first trimester; prenatal diagnosis; twin pregnancy; ultrasound

Due to the widespread use of assisted reproductive techniques, the incidence of twins has increased sharply in China from 2.0% to 5.0% between 1990 and 2014.[1]Compared with singleton pregnancies, the prevalence of structural anomalies is higher in twins overall,[2–4] and even higher in monochorionic (MC) twins.[4–6]

Our team has demonstrated that first-trimester ultrasound scanning is of significant clinical value in detecting fetal structural anomalies earlier in an unselected low-risk singleton population.[7] Standard first-trimester ultrasound examination revealed 56.5% (13/23) of major structural anomalies, including central nervous system defects, congenital heart defects, and abdominal wall defects.[7] These results were in keeping with a systematic review,[8] which assessed diagnostic accuracy of first-trimester ultrasound for the detection of congenital anomalies in singleton pregnancies. In this review, the pooled estimate for the detection of major abnormalities in low-risk or unselected populations (19 studies, 115,731 fetuses) was 46.1% (95% CI, 36.9–55.5%), while for all abnormalities in low-risk or unselected populations (14 studies, 97,976 fetuses), it was 32.4% (95% CI, 22.5–43.1%); finally, in high-risk populations (6 studies, 2841 fetuses), it was 61.2% (95% CI, 37.7–82.2%). When it comes to twin pregnancies, there have been few large studies assessing the diagnostic accuracy of ultrasound for detecting structural anomalies in the first trimester,[9,10] and the detection rate was 27.3%–36.5%.

Several studies have also analyzed the association between ultrasound manifestations such as nuchal translucency (NT) or crown–rump length (CRL) discordance and adverse perinatal outcomes.[11–16] Some studies concluded that NT or CRL discordance were not significantly different between twin-to-twin transfusion syndrome (TTTS) cases and non-TTTS pregnancies,[11–13] while others found that intertwin NT or CRL discordance were associated to adverse outcomes such as TTTS, intrauterine fetal death, and intrauterine growth restriction, but they had little predictive value.[14–16] NT above the 95th centile was found to be significantly associated with anomalies in singleton pregnancies.[17] Two European series demonstrated that in twin pregnancies with high intertwin CRL discordance and increased NT, the incidence of fetal defects was increased, showing that this result can be extrapolated to twins, although their predictive performance was poor.[9,10] However, there are no large studies on this issue in Chinese population yet. Also, previous studies did not clarify the predominant defects detected in cases with an increased NT or CRL.

The aims of this study were, firstly, to evaluate the diagnostic accuracy of first-trimester ultrasound scan in detection of fetal anomalies in twin pregnancies in China; and secondly to assess the association between CRL or NT discordance and fetal structural anomalies in twins.

Material and Methods

This was a retrospective study over a 5-year period from January 2012 to December 2016. The study

included all twin pregnancies booked at Beijing Obstetrics and Gynecology Hospital, a tertiary hospital, for routine antenatal care in the first trimester. Women who were referred to us from other hospitals for further expert consultation were excluded to eliminate referral bias. The study was approved by the Ethics Committees of the Beijing Obstetrics and Gynecology Hospital, Capital Medical University. A waiver of informed consent was approved by the committee, as this was a retrospective study.

In our hospital, we offered routine first-trimester and second-trimester anomaly scans for booked pregnant women. The ultrasound examinations were undertaken using Voluson E8 and Voluson 730 (GE Healthcare, Austria), HI VISION Preirus and HI VISION Ascendus (HITACHI, Japan), and IU22 (PHILIPS, Netherlands).

All first-trimester scans were performed transabdominally in the 11–13^{+6} weeks of gestational age window. Sonographers who performed first-trimester scans in this study received specialized training, and obtained certification according to local medical regulations. All of them have at least 3 years of clinical experience. When a fetal structural anomaly was suspected and transabdominal ultrasound was not satisfactory, with the agreement of the pregnant woman, transvaginal scan was performed to further confirm the diagnosis. Our scanning protocol for assessment of fetal anatomy is consistent with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) first-trimester scan guideline from 2013,[18] before that we followed our local protocol. In brief, ultrasound assessment consisted of sagittal and transverse views. Sagittal views demonstrated nasal bone, spine, and measuring fetal CRL and NT thickness, whereas transverse views demonstrated the presence of skull and symmetrical hemispheres and choroid plexuses, left-sided heart and symmetrical lungs in the chest, the presence of stomach and bladder, abdominal insertion of the umbilical cord, integrity of anterior abdominal wall, and the presence of 4 limbs with 3 segments. Detailed examination of intact lips, eyes with lens, symmetrical four-chamber and three vessels, and vertebrae and overlying skin, kidneys, hands, and feet with normal orientation were not part of routine assessment in this study. Chorionicity was diagnosed by the presence of a λ-sign or T-sign,[19] whereas diamnionicity was defined by the presence of amniotic septation,[20] and further confirmed at birth.

A routine second-trimester (anomaly) scan (which was basically consistent with AIUM standard fetal anatomic survey) was performed in all cases around 22 weeks of gestation. Scanning protocol is consistent with the ISUOG routine mid-trimester scan guideline[21] and Chinese ultrasound scanning guideline, including: sagittal and transverse views of spine to examine complete spine with intact skin covering; transventricular, transthalamic, and transcerebellar plane to examine intact cranium, cavum septi pellucidi, midline falx, thalami, ventricles, cerebellum, vermis, and cisterna magna in the head; medial facial profile plane to examine nasal bone and exclude micrognathia; transverse and coronal views in the face to exam upper lip, nose and nostrils, orbits and lenses; transverse planes through the heart including four-chamber view, outflow tracts and three-vessel (trachea) view to exam chest, lungs, and heart and exclude diaphragmatic hernia; transverse planes of abdomen to examine stomach, liver, bowel, kidneys, abdominal wall, and umbilical cord insertion, pelvis, bladder, and umbilical arteries; systematic examination of limbs to examine the length, shape of 3 bones of both legs and arms, to examine both feet and both hands, and their relationships. Counting fingers or toes and examination of the genitalia was not a compulsory part of the protocol. If a specific abnormality was suspected, the pregnant woman would be referred to a specialist according to Chinese ultrasound scanning guideline.

Fetal echocardiography was routinely arranged for monochorionic twins in the second trimester.

All ultrasound and patients' data were entered into a local database at the time of scan. Pregnancy outcomes, fetal anomalies, and detailed postnatal examinations were obtained by retrieving medical files from the hospital's computerized information system.

In this study, when we assessed the performance of ultrasound in the detection of fetal structural anomalies, we excluded conjoined twins and twin-reversed arterial perfusion sequence (TRAPS). Since it was hard to measure NT and CRL accurately when complicated with these 2 complications, they were excluded from fetal structural anomalies in the statistical analysis.

The diagnostic performance of first-trimester ultrasound was then classified and analyzed in

2 different ways. Firstly, we divided fetal structural anomalies into 7 groups based on different anatomical systems[9]: central nervous system, face, cardiovascular, gastrointestinal, renal, skeletal, miscellaneous (cases that did not fit into any groups above or with multiple anomalies). Secondly, according to the scheme proposed by Syngelaki,[17] we divided fetal structural anomalies into 3 groups: always detectable, potentially detectable, and undetectable.

Prenatal diagnosis and genetic counseling were referred when an increased NT or a major structural anomaly was found. Prenatal consultants would discuss and provide genetic test. Fetal echocardiography was arranged in the second trimester to rule out heart defects. When CRL discordance was detected, obstetricians will discuss the elevated risk of complications and adverse pregnancy outcomes with the patient, including fetal demise and TTTS in monochorionic-diamniotic (MCDA) twins.

Final diagnosis of fetal structural anomalies was based on postnatal examinations in live birth cases, and based on the last ultrasound examination results and general observation in miscarriage, pregnancy termination, or intrauterine fetal death cases. We excluded normal variants such as aberrant right subclavian artery and persistent left superior vena cava. We also excluded isolated ear deformities, isolated genitalia deformities, and isolated abnormal digits because these structures were hard to detect and the diagnosis of them were not compulsory during pregnancy in Chinese and ISUOG guidelines.

The CRL and NT discordance were compared in pregnancies with or without fetal structural anomalies in MC and dichorionic (DC) twins separately, in percentage terms as [(larger CRL - smaller CRL)/larger CRL] × 100 and [(larger NT- smaller NT)/larger NT] × 100 in %, respectively.

Increased NT was defined as NT ≥95th centile; NT ≥99th centile was also analyzed in the study. Increased NT itself was not considered to be a structural anomaly.

Furthermore, we compared inter-twin CRL discordance ≥10% and NT ≥20% in pregnancies with or without fetal structural anomalies in MC and DC twins separately, as definition of inter-twin discordance recommended in twin pregnancy guideline.[19]

Potential independent variables, which might be associated with fetal structural anomalies including advanced maternal age, mode of conception, parity, adverse obstetric history, CRL discordance ≥10%, NT discordance ≥20%, and "either fetus" or "both fetuses" with increased NT.

Distributions of the continuous variables were assessed using Shapiro–Wilk test. Differences between cases with and without fetal structural anomalies were initially evaluated using chi-squared test for categorical variables, t-test for normally distributed continuous variables, and Kruskal–Wallis test for non-normally distributed continuous variables. We then assessed the potential independent variables for detecting fetal structural anomalies using step-wise forward logistic regression. Only the variables that were significant in both univariate and multivariate analyses were included in the final model. No missing imputation technique was required because missing values were < 1% for all variables. Sensitivity and specificity were calculated by using area under the receiving operator characteristic curve (AUC) to assess the detecting accuracy of the variables associated with fetal structural anomalies. A P value < .05 was considered to be statistically significant. SPSS Statistics v.19 (IBM Co., USA) software was used for the analysis.

Results

During the study period (January 2012–December 2016), a total of 1442 women with twin pregnancies were included in the study, including 1190 DC, 239 MCDA, and 13 monochorionic-monoamniotic (MCMA) twins (Figure 1). Over the 5 years, the number of twin pregnancies has increased, from 153 (1.2% of all pregnancies) to 384 (2.6%, Table 1). Exactly 45.7% (659/1442) conceived naturally, while 54.3% (783/1442) conceived by in vitro fertilization including by intra-cytoplasmic sperm injection. The pregnancy outcomes of the 1442 women are shown in Table 2. Other general characteristics are presented in Table 3. In MCDA twins, 9.6% (23/239) were diagnosed as TTTS in our study.

Overall, fetal abnormalities were identified in 3.6% of total cases (52/1442), 2.7% (32/1190) in DC, and 7.9% (20/252) in MC twin pregnancy. We diagnosed 29 cases at the first trimester scan, including all (12/12) of the conjoined twins and TRAPS.

Figure 1. Flow chart of the study. A total of 1442 women with twin pregnancies were included in the study. Excluding conjoined twins (8 women) and TRAPS (4 women), there were 40 women (45 fetuses) with fetal structural anomalies.

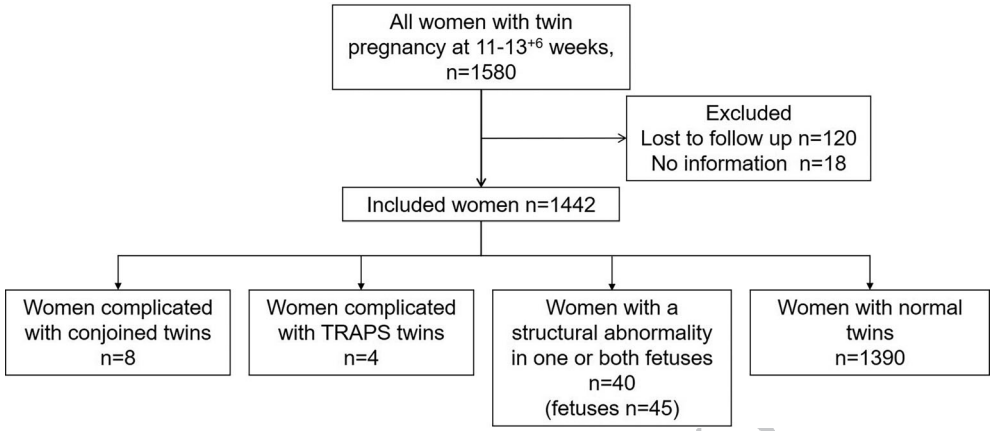

Table 1. Proportion of Women With Twin Gestation per Year

	2012	2013	2014	2015	2016	Total
Twin	153	278	319	308	384	1442
All	12,488	13,903	17,429	12,255	15,030	71,105
Percentage	1.2%	2.0%	1.8%	2.5%	2.6%	2.0%

Table 2. Pregnancy Outcomes of the 1442 Women Included in the Study

Pregnancy Outcomes	Women (n)	Both Fetuses (n)	One Fetus (n)
Miscarriage	50	48	2
Pregnancy termination	36	14	22
Intrauterine death	51	17	34
Live births	1359	1305	54
Total	1442	1384	58[a]

[a]In 22 women, 1 fetus underwent selected pregnancy termination, but in 2 women this led to pregnancy loss of both twins; In 34 women, intrauterine death happened in 1 fetus, but in 2 women this led to pregnancy loss of both twins.

Excluding conjoined twins and TRAPS, fetal structural anomalies were founded in 40 women (45 fetuses) in our study. In 3 DC, 1 MCDA, and 1 MCMA twin pregnancies, both fetuses had structural anomaly. The detection rate of twins with fetal structural anomalies was 42.5% (17/40) per pregnancy, while the rate was 37.8% (17/45) per fetus. When we divided these cases by chorionicity, the detection rate was 37.1% (13/35) per fetus in DC twins and 40.0% (4/10) per fetus in MC twins. The detection rate in the first trimester was 100% for anencephaly, bilateral renal agenesis associated with megacystis, thanatophoric dysplasia, abdominal wall defects, and cystic hygroma, but none for facial, some cardiovascular, gastrointestinal, renal, and nonlethal skeletal anomalies (Tables 4 and S1). A total of 34 patients have undergone invasive testing (Chorionic villus sampling: 3 cases; Amniocentesis: 28 cases; and Cordocentesis: 3 cases). There were 17 twins with structural anomalies who have undergone invasive testing; in 6 fetuses of 4 twins (3 DC, 1 MCDA) chromosomal aberration was diagnosed. Both fetuses in the MCDA twin were diagnosed as Turner's syndrome. One fetus was diagnosed as Down's syndrome, and the co-twin was diagnosed as partial deletion of Chromosome 21 in a DC twin.

Table 3. General Characteristics of the Study Population (N = 1442); Data Are Given as Mean (SD) or n (%) as Indicated

Variables	Mean or n	SD or %
Mean maternal age (SD), years	32.2	3.8
Year of scan, n, n/N		
2012	153	10.6
2013	278	19.3
2014	319	22.1
2015	308	21.3
2016	384	26.6
Mode of conception, n, n/N		
Natural	659	45.7
In vitro fertilization	783	54.3
Parity, n, n/N		
Nulliparous	1273	88.3
Parous	169	11.7
Adverse obstetric history,[a] n, n/N	61	4.2
Chorionicity and amnionicity, n, n/N		
DC	1190	82.5
MCDA	239	16.6
MCMA	13	0.9

[a]Adverse obstetric history is defined as 2 or more miscarriages, stillbirth, neonatal death, and structural or chromosomal anomaly in the previous pregnancy.

In the other 2 DC twins, 1 of each twin was diagnosed as Turner's syndrome mosaic and Down's syndrome, respectively. There were 17 twins without structural anomalies who have undergone invasive testing; in 9 fetuses of 6 twins (5 DC, 1 MCDA) a chromosomal aberration was found. In a DC twin pregnancy, both fetuses were diagnosed as Trisomy 21, whereas in another DC twin pregnancy, 1 fetus was diagnosed as T18. The MCDA twin and the left 4 fetuses of 3 DC twins were diagnosed as nonpathogenic chromosomal structural aberration (translocation, deletion, or inversion), and all of them were born alive.

In the absence of a chromosomal aberration or an isolated structural anomaly, 1.7% (4/232) of MC twin pregnancies were associated with NT ≥95th centile, none of them ended up with 2 live births. On the contrary, 1.5% (17/1158) of DC twin pregnancies were associated with NT ≥95th centile, 15 of them ended up with 2 normal babies, only 2 of them had lost 1 fetus.

Of all the structural anomalies excluding conjoined twins and TRAPS, 26.7% (12/45) were in the "always" detectable category and 100% (12/12) of these fetuses were detected in the first trimester; 51.1% (23/45) were in the "potential" detectable category, and we had detected 5 fetuses of them in DC twins, but none in MC twins; while 22.2% (10/45) were in the "never" detectable group and none of them were detected (Table 4).

The routine second-trimester anomaly scan diagnosed a further 23 fetuses (20 women) with structural anomalies, including VSD, cleft lip, unilateral renal agenesis, and abdominal cyst. The specific anomalies detected by second trimester but missed in the first trimester and outcomes are listed in Table 5. The most common anomaly detected by routine second-trimester anomaly scan but missed in the first trimester was cardiovascular anomalies, especially VSD. The overall sonographic diagnostic rate was 92.5% per pregnancy (37/40), 88.9% per fetus (40/45), although the detection rate in the second trimester was not different from that in the first trimester. Unlike low survival rate (11.8%, 2/17) in fetuses with structural anomalies detected by first-trimester ultrasound, survival rate was relatively high in the fetuses diagnosed in second trimester (65.2%, 15/23).

We stratified CRL and NT discordance by fetal structural anomalies and chorionicity. In both DC and MC twins, the incidence of NT discordance ≥20% in twins with structural anomalies was not different from that of twins without structural anomalies. Mean value of NT and CRL discordance, the percentages of CRL discordance ≥10%, NT ≥95th centile, and NT ≥99th centile were larger in twins with structural anomalies than those twin pregnancies without structural anomalies, in both MC twins and DC twins (Table 6).

Univariate analysis showed that CRL discordance ≥10%, NT ≥95th, centile and NT ≥99th centile were associated with fetal structural anomalies, whereas chorionicity was not. Multivariate analysis demonstrated that CRL discordance ≥10% and NT ≥95th centile were associated with fetal structural anomalies, showing the risk of fetal structural anomalies was increased when CRL discordance ≥10% (OR 3.1, 95%CI 1.5–6.3) and NT ≥95th centile (OR 20.0, 95%CI 9.0–44.2) were present.

CRL discordance and NT thickness in twins with and without fetal structural anomalies plotted according to CRL are shown in Figures S1–S4. The AUC of CRL discordance ≥10% in detecting fetal

Table 4. Number of Fetal Structural Anomalies Detected by Ultrasound in DC and MC Twin Pregnancies in the First Trimester; Data Are Given as n/N (% per Fetus) as Indicated

	First-Trimester Ultrasound Detection	
	DC	MC
Anomaly	**n/N (% per Fetus)**	**n/N (% per Fetus)**
Classified by anatomical systems		
Central nervous system	1/2 (50.0)	0/1 (0.0)
Anencephaly	1/1 (100.0)	—
Severe ventriculomegaly	0/1 (0.0)	0/1 (0.0)
Face	0/2 (0.0)	0/1 (0.0)
Cleft lip	0/1 (0.0)	0/1 (0.0)
Cleft lip and palate	0/1 (0.0)	—
Cardiovascular	2/8 (25.0)	0/2 (0.0)
Single ventricle	0/1 (0.0)	—
Tetralogy of Fallot	0/1 (0.0)	—
Mitral valve dysplasia	0/1 (0.0)	—
AVSD	1/2 (50.0)	—
VSD	0/2 (0.0)	0/2 (0.0)
Tricuspid dysplasia + VSD	1/1 (100.0)	—
Gastrointestinal	0/3 (0.0)	0/0 (0.0)
Gastrointestinal obstruction	0/1 (0.0)	—
Duodenal atresia	0/1 (0.0)	—
Congenital atresia of esophagus	0/1 (0.0)	—
Renal	0/5 (0.0)	1/2 (50.0)
Unilateral renal agenesis	0/2 (0.0)	—
Bilateral renal agenesis	—	0/1 (0.0)
Severe hydronephrosis	0/1 (0.0)	—
Duplex kidney	0/2 (0.0)	—
Megacystis + Bilateral renal agenesis	—	1/1 (100.0)
Skeletal	1/2 (50.0)	0/1 (0.0)
limb angulation	0/1 (0.0)	—
Collapse of spine	—	0/1 (0.0)
Thanatophoric dysplasia	1/1 (100.0)	—
Miscellaneous	9/13 (69.2)	3/3 (100.0)
Ventriculomegaly + VSD + diaphragmatic hernia	0/1 (0.0)	—
Cleft lip + congenital atresia of esophagus + exomphalos + Single ventricle + double outlet of right ventricle + pulmonary stenosis + umbilical cord cyst	0/1 (0.0)	—
Anencephaly + Exocardia + Gastroschisis	1/1 (100.0)	—
Limb body wall complex	1/1 (100.0)	—
Fetal hydrops + exomphalos	1/1 (100.0)	—
Gastroschisis	1/1 (100.0)	1/1 (100.0)
Exomphalos	1/1 (100.0)	—
Cystic hygroma	2/2 (100.0)	2/2 (100.0)
Abdominal cyst	2/4 (50.0)	—
Classified by Syngelaki (17)		
Always detectable	8/8 (100.0)	4/4 (100.0)
Potentially detectable	5/19 (26.3)	0/4 (0.0)
Never detectable	0/8 (0.0)	0/2 (0.0)

Table 5. Number of Survived Fetus With Structural Anomalies Classified by Anatomical Systems in Twin Pregnancies Detected by First-Trimester, Second-Trimester Scan but Missed in the First Trimester or at/Only After Birth; Data Are Given as n/N (% per Fetus) as Indicated

	Detected in the First Trimester	Detected in the Second Trimester but Missed in the First Trimester	Detected only at/After Delivery
Anatomical Systems	**n/N (% per fetus)**	**n/N (% per Fetus)**	**n/N (% per Fetus)**
Central nervous system	0/1 (0.0)	0/1 (0.0)	1/1 (100.0)
Anencephaly	0/1 (0.0)[a]	—	—
Severe ventriculomegaly	—	0/1 (0.0)	1/1 (100.0)
Face	0/0 (0.0)	2/3 (50.0)	0/0 (0.0)
Cleft lip	—	1/2 (50.0)[a]	—
Cleft lip and palate	—	0/1 (0.0)[a]	—
Cardiovascular	0/2 (0.0)	4/7 (71.4)	1/1 (100.0)
Single ventricle	—	1/1 (100.0)	—
Tetralogy of Fallot	—	1/1 (100.0)	—
Mitral valve dysplasia	—	0/1 (0.0)[a]	—
AVSD	0/1 (0.0)[a]	0/1 (0.0)	—
VSD	—	2/3 (66.7)	1/1 (100.0)
Tricuspid dysplasia + VSD	0/1 (0.0)[a]	—	—
Gastrointestinal	0/0 (0.0)	2/2 (100.0)	1/1 (100.0)
Gastrointestinal obstruction	—	1/1 (100.0)	—
Duodenal atresia	—	1/1 (100.0)	—
Congenital atresia of esophagus	—	—	1/1 (100.0)
Renal	0/1 (0.0)	3/4 (75.0)	2/2 (100.0)
Unilateral renal agenesis	—	2/2 (100.0)	—
Severe hydronephrosis	—	1/1 (100.0)	—
Duplex kidney	—	—	2/2 (100.0)
Megacystis + bilateral renal agenesis	0/1 (0.0)[a]	—	—
Bilateral renal agenesis	-	0/1 (0.0)[a]	—
Skeletal	0/1 (0.0)	1/2 (50.0)	0/0 (0.0)
limb angulation	—	1/1 (100.0)	—
Collapse of spine	—	0/1 (0.0)	—
Thanatophoric dysplasia	0/1 (0.0)[a]	—	—
Miscellaneous	2/12 (16.7)	3/4 (75.0)	0/0 (0.0)
Ventriculomegaly + VSD + diaphragmatic hernia	—	1/1 (100.0)	—
Cleft lip + congenital atresia of esophagus + exomphalos + Single ventricle + double outlet of right ventricle + pulmonary stenosis + umbilical cord cyst	—	0/1 (0.0)[a]	—
Anencephaly + Exocardia + Gastroschisis	0/1 (0.0)[a]	—	—
Limb body wall complex	0/1 (0.0)[a]	—	—
Fetal hydrops + exomphalos	0/1 (0.0)	—	—
Gastroschisis	0/2 (0.0)[a]	—	—
Exomphalos	1/1 (100.0)	—	—
Cystic hygroma	0/4 (100.0)[a]	—	—
Abdominal cyst	1/2 (50.0)[a]	2/2 (100.0)	—
Total	2/17 (11.8)	15/23 (65.2)	5/5 (100.0)

[a]Termination of pregnancy was elected; in the 2 cases of gastroschisis, 1 of them selected termination of pregnancy.

structural anomalies was 0.63 (95%CI 0.53–0.73), sensitivity was 40.0% (95%CI 33.2–48.6), and specificity was 86.8% (95%CI 85.7–87.6). The AUC of NT ≥95th centile in detecting fetal anomalies was 0.65 (95%CI 0.55–0.76), sensitivity was 32.5% (95%CI 26.6–41.4), and specificity was 98.2% (95%CI 97.7–98.4).

Table 6. CRL Discordance and NT Discordance in Relation to Fetal Structural Anomalies, Excluding Conjoined Twins and TRAPS

	MC Twins			DC Twins		
Between Twin Discordance of:	**Anomaly (N = 8)**	**No Anomaly (N = 232)**	***P* Value**	**Anomaly (N = 32)**	**No Anomaly (N = 1158)**	***P* Value**
Mean CRL (SD), %	9.3 (4.8)	4.9 (4.3)	.011	7.5 (6.8)	5.2 (4.3)	.036
Mean NT (SD), %	41.0 (30.2)	19.6 (15.2)	.045	34.9 (29.1)	20.5 (14.4)	.004
CRL discordance ≥10% (n, %)	4 (50.0)	29 (12.5)	.012	12 (37.5)	155 (13.4)	.000
NT discordance ≥20% (n, %)	6 (75.0)	109 (47.0)	.230	19 (59.4)	554 (48.1)	.208
NT ≥95th centile (n, %)	3 (37.5)	5 (2.2)	.000	10 (31.3)	20 (1.7)	.000
NT ≥99th centile (n, %)	2 (25.0)	5 (2.2)	.007	7 (21.9)	7 (0.6)	.000

In the setting of CRL discordance ≥10% , 40% (16/40) of twins with structural anomalies were found, in which the predominant fetal structural anomalies were cardiovascular defects, abdominal wall defects, and central nervous system defects. In the setting of NT ≥95th centile, 32.5% (13/40) twins with structural anomalies were found, in which the predominant fetal structural anomalies were cardiovascular defects, cystic hygroma, and abdominal wall defects. The AUC for detecting structural anomalies by CRL discordance ≥10% was 0.65.

Discussion

In our study, we illustrated the detection rate and the survival rate of fetal structural anomaly by first-trimester ultrasound and routine second-trimester anomaly scan in twin pregnancies. We have proved the association between CRL discordance ≥10%, NT ≥95th centile, and fetal structural anomalies. Furthermore, we listed the predominant fetal structural anomalies in the setting of CRL discordance or increased NT.

The proportion of DC twins of our study was higher than other studies.[9,10] The possible reason was the growing success rate of assisted reproductive technique in our center.

In our study, the detection rate of fetal structural anomaly by first-trimester ultrasound was 42.5% per pregnancy in twin pregnancies. This result was similar to but a little higher than that of D′Antonio's study.[9] When comparing with a recent large study of Syngelaki,[10] the detection rate of fetal structural anomaly was higher in DC twins, but lower in MC twins. This may be due to differences in study setting and different incidences of fetal structural anomalies. This could also be related to the methodology applied—we had excluded conjoined twins and TRAPS from fetal structural anomalies when analyzing diagnostic performance in MC twins. Nevertheless, our findings were roughly similar to those of Syngelaki,[10] Sperling,[23] and D′Antonio[9]: the diagnostic performance was good for major structural anomalies such as anencephaly, megacystis, abdominal wall defects, but was poor for facial, some cardiovascular, gastrointestinal, renal, and nonlethal skeletal anomalies. This finding was also comparable to our earlier study and a systemic review in singletons.[7,24]

The detection rate of twins with fetal structural anomalies was 92.5% when routine second-trimester anomaly scan was added to first-trimester ultrasound. In China, all singletons or twin pregnancies would receive a routine fetal anatomic screening (which was basically consistent with AIUM standard fetal anatomic survey) in the second trimester according to Chinese ultrasound scanning guideline. The survival rate was much higher in fetuses with structural anomalies detected by routine second-trimester anomaly scan than those detected by first-trimester ultrasound. This was similar to Kenkhuis.[25] In their study, they have reported that after first trimester and second trimester diagnoses, parents elected to terminate the pregnancy in 54% and 24% of cases, respectively.[25] This was probably due to different types of anomalies. Compared with second trimester, the structural anomalies detected in the first trimester were more severe and lethal, such as anencephaly, bilateral renal

agenesis associated with megacystis. Therefore, screening structural anomalies using standard protocol in the first trimester was of significant clinical relevance.

CRL discordance has become an important topic in twin studies. Studies have suggested that in the management of twin pregnancy with CRL discordance more than 10%, referral to a fetal medicine expert should be considered.[19] Other studies suggested that increased CRL discordance was at significantly higher risk of adverse outcomes such as preterm delivery, fetal loss, and birth weight discordance in twins,[14,15,26–29] but CRL discordance alone cannot be used to predict these adverse outcomes.[14,15] A few studies have found that CRL discordance was associated with structural anomalies.[9,10,19,30,31] In our study, univariate analysis showed that CRL discordance ≥10% was associated with fetal structural anomalies, and the association was still significant by further multivariate analysis. The most predominant fetal structural anomalies with CRL discordance ≥10% were cardiovascular defects and abdominal wall defects. Therefore, increased CRL discordance seems to indicate increased risk of fetal structural anomalies such as cardiovascular defects and abdominal wall defects in twins, but its efficacy is very limited.

It has been proved that increased NT was associated with fetal structural anomalies in singletons.[17,32,33] The same association has been found in twins when increased NT was defined as NT ≥99th centile.[10,34] Our study showed that increased NT was more common in twins with fetal structural anomalies, either in DC or MC twins. NT ≥95th centile was relatively more closely associated with fetal structural anomalies than NT ≥99th centile in twins. Our study has also showed that NT discordance ≥20% was not associated with fetal structural anomalies, although it has been found to be related to other adverse pregnancy outcomes in other studies, especially in MC twins.[23,35] Therefore, compared with NT ≥99th or NT discordance ≥20%, NT ≥95th centile seems to be a better indicator for fetal structural anomalies in twins. As in singletons,[17] the most common associated fetal structural anomaly was cardiovascular defects when NT ≥95th centile was found in one or both twins. However, the AUC, sensitivity, and specificity of NT ≥95th centile for detecting fetal structural anomalies were not high enough for clinical utility.

We assumed that isolated increased NT might be associated with adverse outcomes in MC twins, but does not have the same effect in DC twins. This result was concluded from our limited number of cases; however, our findings were still similar to a recent study, which concluded that increased NT was associated with a substantially increased risk of fetal loss or need for endoscopic laser surgery at <20 weeks of gestation in MCDA twins, but was not significantly different between those with 2 survivors and those with adverse outcome in DC twins.[36]

Our study showed that CRL discordance and NT discordance in twins with fetal structural anomalies were larger than twins without anomalies, and it seemed more obvious in MC twins than in DC twins, although monochorionicity was found not to be associated with fetal structural anomalies by univariate or multivariate analysis. This was not consistent with D′Antonio,[9] and may be due to no association; or lack of statistical power due to the relatively low incidence of fetal structural anomalies in MC twins in the present study.

There are some limitations of this study. The retrospective study design was one of the limitations; we had to exclude some cases due to missing data during the study period, which might lead to bias. In cases of pregnancy termination, miscarriage, or intrauterine death, it is possible that some minor defects were left undetected with first-trimester ultrasound, which could not be confirmed by second-trimester scan or at delivery. The strengths of our study include the large sample, and the fact that scanning was based on standard examination protocol for detection of structural abnormalities in the first trimester. Very detailed assessment of neonatal and infant records means that the risk of poor ascertainment of anomalies should be low. We also excluded referred cases to eliminate referral bias.

We have proved the association between CRL discordance, increased NT and fetal structural anomalies in twin pregnancies, which might indicate the higher risk of fetal structural anomalies. Although the efficacy was limited to detect structural anomalies, we still recommend more detailed anatomic survey in both MC and DC twin pregnancies during the entire pregnancy period in the setting of CRL discordance and increased NT.

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