Predictive values of first trimester ultrasound screening for twin-to-twin transfusion syndrome and selective intrauterine growth restriction in monochorionic twin pregnancies

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Abstract

Background: Monochorionic diamniotic (MCDA) twins have a substantially higher risk for perinatal morbidity and mortality due to the presence of placental vascular anastomoses between the twins.

Objectives: The primary purpose of this research was to confirm the accuracy of first trimester ultrasonography in predicting selective intrauterine growth restriction (SIGR) and twin-to-twin transfusion syndrome (TTTS) in monochorionic twin pregnancies using the triad of nuchal translucency (NT), cord insertion and inter-twin discordance in foetal size.

Patients and methods: This was a prospective cohort study that included 31 pregnant women who were carrying monochorionic twins during the first trimester. The research was carried out at a foetal medicine unite, Obstetrics and Gynecology Department, South Valley University Hospital. The duration of the study ranged from 18 to 24 months.

Results: the mean difference in NT can determine TTTS with fair sensitivity (73.2%) and high specificity (100%) in twins ($p<0.001$). Likewise, mean difference in CRL can determine TTTS with fair sensitivity (73.1%) and high specificity (100%) in twins ($p<0.001$).The mean difference in NT can determine sIUGR with high sensitivity (100%) and fair specificity (73.2%) in twins ($p<0.001$). Likewise, mean difference in CRL can determine sIUGR with high sensitivity (100%) and fair specificity (73.1%) in twins ($p<0.001$).

Conclusion: we have demonstrated that NT and CRL were significantly higher in TTTS group, and NT and CRL were respectively identified as the predictive markers for sIUGR and TTTS.

Keywords: monochorionic twin pregnancies; sIUGR; perinatal morbidity**.**

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Introduction

The risk in twin pregnancies is higher than singleton pregnancies with monochorionic twins demonstrating the highest risk. Approximately 30% of twins are monochorionic, however, they account for 75% of all twin problems. Twin-to-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR), and twin anaemia polycythaemia sequence (TAPS) are some of the issues that can arise. The most severe problem in monochorionic twin is TTTS which usually occurs around 20 weeks gestation and if left untreated it is associated with a perinatal loss rate up to 90%. **(Crowther et al., 2001).**

To detect these issues, most of clinics perform an ultrasound every two weeks. Detecting a high risk of monochorionicity early in the pregnancy would allow for more effective surveillance. Although ultrasonographic features offer a decent sensitivity and specificity in terms of allocating risk of severe TTTS, such screening is nevertheless linked with a high proportion of false positives and false negatives, with a detection rate of just 52%. **(Kagan et al., 2007)**.

Till now, we are unable to predict accurately which twins will develop complications or how severe they will be. Several studies are done using different ultrasound soft markers; however, none of these markers are effective enough to be used in the continuous obstetric surveillance of MCDA twin pregnancies (Mogra et al, 2020). The primary purpose of this research was to confirm the accuracy of first trimester ultrasonography in predicting selective intrauterine growth restriction (SIGR) and twin-to-twin transfusion syndrome (TTTS) in monochorionic twin pregnancies using the triad of nuchal translucency (NT), cord insertion and inter-twin discordance in foetal size.

Patients and methods

A total of 31 pregnant women who were carrying monochorionic twins at the beginning of the first trimester took part in this prospective cohort research. The research was carried out at a foetal medicine unite, Obstetrics and Gynecology department, South Valley University Hospital. The duration of the study ranged from 18 to 24 months.

Inclusion criteria: Monochorionic twin pregnancies at first trimester

Exclusion criteria: Women were excluded from the study if they had one or more of the following: Confirmed anomalies affecting amniotic fluid as GIT anomalies and premature rupture of membrane "PROM" in the course of the study

Samples: *Sample size calculation:* Sample size will be calculated using the Steven K.Thompson equation. Total sample size is 30 cases.

$$N = \frac{N \times P (1-P)}{[N-1 \times (d^2 \div z^2) + P (1-P)]}$$

N = Population size, D = margin of error; 0.05, P = P value; 0.05 and Z = confidence level at 95% is 1.96

Study tools: Using the ultrasound machine "Voluson P8"; all women with monochorionic twins at first trimester had undergone screening for complications of monochorionicity by assessment the triad of: Differences in nuchal translucency (NT), differences in crown rump length (CRL) and cord insertion site, in addition to first trimester screening for aneuploidy.

At 20 weeks gestation, these women had undergone screening for complications of monochorionicity namely TTTS and sIUGR, in addition to routine second trimester anomaly scan. This is to validate the first trimester ultrasound screening for complications of monochorionicity using the triad of NT, CRL and cord insertion. Prenatal ultrasound diagnosis of TTTS requires two criteria ***(*Simpson, 2012)***; Stage I TTTS is defined by the presence of both **(Quintero et al., 1999)**: (1) MCDA pregnancy (2) In one sac, there is oligohydramnios with a maximum deepest pocket (MVP) of 2 cm, and in the other sac, there is polyhydramnios with an MVP of >8 cm. Prenatal ultrasound diagnosis of sIUGR requires two criteria***(*Valsky et al., 2010)***: (1) Presence of monochorionic diamniotic (MCDA) pregnancy (2) Expected fetal weight (EFW) < 10^{th} centile in one fetus, or inter-twin EFW discordance > 25% calculated as [(larger twin-smaller twin)/larger twin].

Research outcome measures: Our outcome measure was to test the predictivity of first trimester ultrasound screening of monochorionic twin for detection of TTTS and sIUGR

Ethical consideration: The study approved by the Institutional Review Board of the SVU-faculty of medicine. An informed consent taken from all participants before entry into the study.

The ethical approval code is: SVU-MED-OBG024-2-2020-4-35

Statistical Analysis

The collected data were tabulated and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1. Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median and 1st& 3rd inter-quartile range, while they were done for categorical data as number and percentage. Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non-parametric data. Inferential analyses were done for qualitative data using Chi square test for independent groups. Fischer exact test; used to study the association between two qualitative variables for 2x2 tables when the expected cell count of more than 25% of cases was less than 5. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance. Receiver operating characteristic (ROC) analysis: It is graphical plot of sensitivity against one minus the specificity (false positive rate) for different cutoffs. The optimal cutoff value was determined using Youden index J that is the farthest point on ROC curve from the diagonal line of equality [maximum (sensitivity + specificity)- 1]. Total area under ROC curve (AUC or AUROC) was a measure of the overall accuracy of a test. The larger the AUC, the better the overall performance of a test to correctly discriminate between diseased and non-diseased subjects. Test characteristics were estimated by ROC curve and included best cutoff value, AUC, its standard error (SE), and P-value. In addition, to assess the effectiveness of the test, estimates as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated at the optimal cutoff.

Results

This was a prospective cohort study conducted on 31 pregnant women with monochorionic twin pregnancies at the time of first-trimester.

Table 1. Distribution of studied cases as per demographic characteristics

Variables		Study group (n = 31)	
		N	%
Maternal age (years)	Mean± SD	27.61± 4.08	
	Median	28.0	
	Range	21.0- 35.0	
Occupation	Housewife	29	93.5%
	Teacher	2	6.5%
Residence	Rural	3	9.7%
	Urban	28	90.3%

N= number, %= percentage, SD: Standard deviation

This table shows that the age of the studied cases ranged from 21 to 35 years with mean ±SD= 27.61± 4.08 years. Regarding occupation, the majority of cases (93.5%) were housewives. Most of cases (90.3%) were from urban areas.

Table 2. Distribution of studied cases as per late first trimester U/S

Variables		Fetus A		Fetus B	
		n	%	n	%
Cord insertion	Central>2 cm from placenta	31	100.0%	18	58.1%
	Marginal <2 cm from placenta	0	0.0%	13	41.9%
NT(mm)	Mean± SD	1.67± 0.23		1.55± 0.18	
	Median	1.60		1.50	
	Range	1.30- 2.20		1.30- 1.90	
CRL (mm)	Mean± SD	65.43± 10.73		64.18± 9.91	

Variables		Fetus A		Fetus B	
		n	%	n	%
	Median	69.0		68.0	
	Range	45.0- 83.0		45.10- 80.0	

N= number, %= percentage, SD: Standard deviation, NT: Nuchal translucency, CRL: Crown-rump length

Table (2) shows distribution of studied cases regarding late first trimester U/S findings. As regards cord insertion, it was central in 100% fetuses A and 58.1% fetuses B, 41.9% fetuses B had marginal insertion. The mean Nuchal translucency in fetus A & B was 1.67± 0.23 mm & 1.55± 0.18 mm respectively. the mean CRL in fetus A & B was65.43± 10.73 mm & 64.18± 9.91 mm respectively.

Table 3. Comparison between cases with TTTS and sIUGR regarding demographic, clinical and US characteristics

Variables		sIUGR group (No. = 5)		TTTS group (No. = 26)		Test value	P-value
		No.	%	No.	%		
Maternal age (years)	Mean± SD	29.20± 2.95		27.31± 4.24		T = 0.948	0.351
Occupation	House Wife	5	100.0%	24	92.3%	FET = 0.411	0.521
	Teacher	0	0.0%	2	7.7%		
Residence	Rural	1	20.0%	2	7.7%	FET= 0.727	0.422
	Urban	4	80.0%	24	92.3%		
Cord insertion in fetus A	Central	5	100.0%	26	100%	FET = 0. 199	1.00
Cord insertion in fetus B	Central	0	0.0%	18	69.2%	FET = 5.66	0.017
	Marginal	5	100.0%	8	30.8%		
Mean difference in NT(mm)	Mean± SD	0.02± 0.04		0.27± 0.16		^{Z}MWU = 3.08	0.002
NT discordance >20%	No	5	100.0%	12	46.2%	FET = 4.91	0.048
	Yes	0	0.0%	14	53.8%		
Mean difference in CRL(mm)	Mean± SD	1.26± 2.20		2.60± 0.55		^{Z}MWU = 2.7	0.007
CRL discordance >10%	No	0	0.0%	11	42.3%	FET = 0.328	0.133
	Yes	5	100.0%	15	57.7%		

The Mann-Whitney test and the Chi-Square test are used to compare groups. p0.05 is regarded statistically significant, p0.01 is considered very statistically significant, SD = standard deviation, and the Mann-Whitney test and the Chi-Square test are used to compare groups.

Table (3) shows comparison between TTTS & sIUGR regarding demographic, clinical and US characteristics. In terms of Cord insertion (p=0.017) and NT discordance >20 percent (p=0.048), there were statistically significant differences between the two groups.

In addition, there were statistically significant variations in mean NT and mean CRL between the two groups. The mean difference in NT and CRL were significantly higher in TTTS group (p=0.002& 0.007 respectively). The MPV value revealed statistically significant increase in cases with TTTS in both fetus A & B (p<0.001). There were no statistically significant differences between the two groups in terms of maternal age, residence ,occupation and CRL discordance >10% (p>0.05).

Table 4. Validity of first trimester ultrasound in prediction of TTTS in monochorionic twin pregnancies

Variables	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
Mean differences in NT (mm)	>1.0	0.935	73.2%	100%	100%	78.9%	<0.001
Mean differences in CRL(mm)	≤ 1.0	0.877	73.1%	100%	100%	78.8%	<0.001
Cord insertion	≤ 1.0	0.846	69.2%	100.0%	100%	76.5%	<0.001

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area Under Curve

By using ROC-curve analysis, the mean difference in NT can determine TTTS with good sensitivity (73.2%) and high specificity (100%) in twins (p<0.001). Likewise, mean difference in CRL can determine TTTS with good sensitivity (73.1%) and high specificity (100%) in twins (p<0.001). Also, cord insertion can determine TTTS with good sensitivity (69.2%) and high specificity (100%) in twins (p<0.001).

Table 5. Validity of first trimester ultrasound in prediction of sIUGR in monochorionic twin pregnancies

Variables	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
Mean differences in NT (mm)	**>0.0**	**0.935**	**100%**	**73.2%**	**78.9%**	**100%**	**<0.001**
Mean differences in CRL(mm)	**≤ 1.0**	**0.877**	**100%**	**73.1%**	**78.8%**	**100%**	**<0.001**
Cord insertion	**≤ 1.0**	**0.846**	**100.0%**	**69.2%**	**76.5%**	**100%**	**<0.001**

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area under Curve

By using ROC-curve analysis, the mean difference in NT can determine sIUGR with high sensitivity (100%) and good specificity (73.2%) in twins (p<0.001). Likewise, mean difference in CRL can determine sIUGR with high sensitivity (100%) and good specificity (73.1%) in twins (p<0.001). Also, cord insertion can determine sIUGR with high sensitivity (100%) and good specificity (69.2%) in twins (p<0.001). Table (5)

Discussion

This was a prospective cohort study was conducted on 31 pregnant women with monochorionic Pregnancies that are twins in the first trimester. The research was carried out at a foetal medicine unite, Obstetrics and Gynecology Department, South Valley University Hospital. The duration of the study ranged from 18-24 months. In this study all the included 31 cases were complicated; 26 cases were complicated by TTTS (83.9 %) and 5 cases were complicated by sIUGR (61.1%). This may be attributed to the small sample size of the study. The age of the studied cases ranged from 21 to 35 years with mean ±SD= 27.61± 4.08 years. Regarding occupation, most cases (93.5%) were housewives. Most of cases (90.3%) were from urban areas.

Our results were supported by study of **Zhu et al.(2021)**, According to them; the current study comprised a total of 98 MDCA pregnancies. The age of the mothers ranged from 20 to 40 years, with a median of 33 years. Also, in the study of **Yamamoto et al. (2013)**, the mean maternal age was 30.7± 5 years. The present study showed that as regard distribution of studied cases regarding late first trimester U/S findings. As regards cord insertion, it was central in 100% fetuses A and 58.1% fetuses B, 41.9% fetuses B had marginal insertion. The mean Nuchal translucency in fetus A & B was 1.67± 0.23 mm & 1.55± 0.18 mm respectively. The mean CRL in fetus A & B was 65.43± 10.73 mm & 64.18± 9.91 mm respectively. As regard distribution of studied cases regarding mean difference and discordance of NT and CRL. The mean difference in NT was 0.23± 0.17 mm with discordance >20 % found in 14 (45.2%) cases. The mean difference in CRL was 1.48± 2.07 mm with discordance >10 % found in 20 (64.5%) cases.

While, in the study of **Matias et al. (2010)**, CRL (SD) was 64 (9.5) mm on average, The average thickness of NT was 1.6 (0.6) mm.
In NT, the mean intertwin difference was 0.36 (0.58) mm, but in CRL, it was 2.96 (2.41) mm. The average ratio of CRL to NT was 1.05. While the average NT to CRL ratio was 1.28 (0.48). (0.04).

In a study conducted by **Kagan et al.(2007)**, CRL discordance was found to be significantly higher in TTTS foetuses, while **El Kateb et al. (2007)** comment in the third arm of their study that when the intertwin CRL discordance was greater than 10%, it had a positive correlation with early TTTS development **(prior to 20 weeks).** Other research, including the first two arms of El Kateb's study, failed to demonstrate statistical significance between intertwin CRL discordance and TTTS progression **(Matias et al., 2010).** Other research has likewise been unable to find statistical significance in the CRL disparity **(Memmo et al., 2012).** In the study in our hands, as regard comparison between cases with and without TTTS regarding demographic, clinical and US characteristics. There were statistically significant differences between the two groups in terms of Cord insertion (p=0.017) and NT discordance >20% (p=0.048). The mean difference in NT and CRL were significantly higher in TTTS group (p=0.002& 0.007 respectively). The MPV value revealed statistically significant increase in cases with TTTS in both fetus A & B (p<0.001). In terms of maternal age, domicile, and occupation, between the two groups, there were no statistically significant differences (p>0.05). In terms of mean NT, there were no statistically significant differences between the two groups. CRL, or CRL discordance >10% (p>0.05). According on our findings, the study of Zhu et al., 2021 According to their findings, there was a significant difference in the NT differential between normal and TTTS pregnancies (P=0.031). The NT discordance between the normal, sIUGR, and TTTS groups was significantly different; also, there was a significant difference between normal and sIUGR (P0.001), normal and TTTS (P0.001), Furthermore, the DV PIV disparity between sIUGR and normal pregnancies was significantly different (P0.001). Furthermore, no significant variations in CRL difference, CRL discordance, or DV PIV discordance were found.

Memmo et al. (2012) studied 242 twin pregnancies, including 102 with TTTS, 36 with sFGR, and 104 without. There were no significant variations in mother age, parity, or median gestational age between the three groups at the first-trimester ultrasound. There was no link between percent CRL difference and percent NT discrepancy (Spearman's rho = 0.042, P = 0.59) or gestational age (Spearman's rho = 0.01, P = 0.15). The difference in NT between sFGR, TTTS, and controls was not statistically significant (P = 0.869), while it was statistically significant in CRL (P 0.001). The CRL difference in the sFGR group (11.9%) was considerably greater than in the TTTS (3.8%) and control (3.5%) groups. The CRL disparity between the TTTS and control groups was not statistically significant (P = 0.12). Our results showed that as regard validity of first trimester ultrasound in prediction of TTTS in monochorionic twin pregnancies; by using ROC-curve analysis, the mean difference in NT can determine TTTS with good sensitivity (73.2%) and high specificity (100%) in twins (p<0.001). Likewise, mean difference in CRL can determine TTTS with good sensitivity (73.1%) and high specificity (100%) in twins (p<0.001).As regard validity of first trimester ultrasound in prediction of sIUGR in monochorionic twin pregnancies; by using ROC-curve analysis, the mean difference in NT can determine sIUGR with high sensitivity (100%) and good specificity (73.2%) in twins (p<0.001). Likewise, mean difference in CRL can determine TTTS with high sensitivity (100%) and good specificity (73.1%) in twins (p<0.001).Our results were supported by study of **Zhu et al.(2021)** with the following other markers from high to low sequence, [ROC area under the curve (AUC) =0.769; 95 percent confidence interval (CI): 0.591 to 0.992] The NT difference was found to be the most effective characteristic for predicting sIUGR.

CRL discordance (AUC =0.534; 95 percent CI: 0.316 to 0.627), CRL difference (AUC =0.503; 95 percent CI: 0.364 to 0.753), DV PIV difference (AUC =0.564; 95 percent CI: 0.412 to 0.758), NT discordance (AUC =0.691; 95 percent CI: 0.425 to 0.786), According to Mogra et al., 2020, NT discordance was similarly the best predictor of TTTS (ROC AUC = 0.79; 95 percent CI 0.58–0.99). The CRL (AUC = 0.51; 95% CI 0.30–0.72) and DV PIV discordance (AUC = 0.60; 95% CI 0.42–0.78) were not predictive. Combining marker performance did not improve (AUC = 0.80; 95 percent CI 0.61–0.99). None of the variables investigated were shown to predict sIUGR: For NT, DV, and CRL, the AUC estimations were 0.34 (95 percent CI 0.17–0.51), 0.36 (0.18–0.54), and 0.54 (0.38–0.70), respectively. According to **Fratelli et al.(2011)**, the area under the ROC curve for the development of TTTS predicted by CRL discordance was 0.52 (95 percent CI 0.38–0.67), while it was 0.50 for NT discordance (95 percent CI 0.35–0.64). In sIUGR pregnancies, NT discordance was much higher. ($p = 0.004$) than in both simple and TTTS pregnancies ($p = 0.003$)Moreover , **Memmo et al.(2012)** according to the ROC analysis, For the prediction of sFGR, The area under the curve was 0.89 (with a 95 percent confidence interval of 0.83–0.95). For TTTS prediction, the area under the curve was 0.58 (with a 95% confidence interval of 0.49–0.66). A CRL discrepancy threshold of 7.12 percent resulted in a sensitivity of 92 percent (95 percent confidence interval (CI) 78–98 percent).

Conclusion:

We have demonstrated that NT and CRL were significantly higher in TTTS group, and NT and CRL were found to be prognostic markers for sIUGR and TTTS, respectively.

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