

A Prospective Study on Perinatal Outcomes of *In Vitro* Fertilization-conceived Dichorionic Diamniotic Twins with Crown–Rump Length Discordancy

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ABSTRACT

Aim: To study the perinatal outcome of dichorionic diamniotic (DCDA) twin pregnancies conceived by *in vitro* fertilization (IVF) with respect to crown–rump length (CRL) discordance at 11–14 weeks.

Materials and methods: This was a prospective observational cohort study conducted over a period of 1 year. All antenatal patients conceived with IVF and DCDA twin gestation were enrolled in the study at 11–14 weeks. They were classified into two groups based on the presence of significant CRL discrepancy of more than or equal to 10% into a discordant and concordant group and followed up till delivery and neonatal period to study the perinatal outcome.

Results: Of the 176 DCDA twins, 30% were discordant for CRL and 70% were concordant for CRL. Primary outcome measures like total pregnancy loss below 24 weeks and preterm birth (PTB) below 32 weeks as well as secondary outcome measures like discordant anomalies, selective fetal growth restriction (FGR), discordant birthweight were significantly more in discordant group.

Conclusion: First-trimester determination of chorionicity is vital for planning antenatal visits and further management of gestation. The significant discrepancy will help us to categorize the dichorionic twins into two groups. Intertwin CRL discordance entails an increased risk of adverse conditions mainly of fetal loss below 24 weeks, selective FGR, and PTB below 32 weeks.

Clinical significance: The CRL discordant twins in IVF-conceived DCDA twins are strongly associated with discordant structural abnormalities and selective FGR at later gestations and thus increasing the incidence of PTB less than 32 weeks in this group. Identification of this group may help in counseling and closer surveillance.

Keywords: Artificial reproductive techniques, Crown–rump length, Discordant, Maternal outcome, Perinatal outcome, Twin pregnancy.

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INTRODUCTION

Twins account for about 1% of all pregnancies.¹ Multiple pregnancies are associated with more maternal and fetal risks compared to singleton pregnancy mainly due to PTB, growth discordance, and fetal anomalies.^{2,3} Growth discordance is a complication unique to multiple gestations. Discordant growth in twins has been associated with PTB, low birth weight (LBW), and FGR.⁴

In DCDA twin pregnancies' growth discordance could be due to genetic factors, and hence discordant anomaly may be the cause of discordance in smaller twins. Similarly, each fetus may have a different growth potential compared to its co-twin and thus one of the twins may be constitutionally small giving rise to the discordant growth picture. It could also be due to uteroplacental factors affecting one fetus only. A significant difference in the weight of the placenta has been observed between concordant and discordant twin pregnancies.⁵

Even though first-trimester growth traditionally has been thought to occur at a constant exponential rate with little biologic variation, intrauterine factors such as abnormal placentation or unequal distribution of uterine blood flow in twin gestations may affect growth earlier than previously thought.^{6,7} Hence, detecting a CRL discrepancy in ultrasound in the first trimester will help in identifying pregnancies that are at risk for adverse perinatal outcomes which is important for patient counseling, surveillance pregnancy management, and choice of the delivery site.

The significance of CRL discordance as a screening parameter and its magnitude as a predictor of pregnancy and perinatal

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complications remains a matter of debate. Although very large differences in CRL have been associated with aneuploidy and anatomic abnormalities, the clinical outcomes of euploid fetuses without major congenital anomalies are not well studied. A few studies have shown the association between CRL discordance in DCDA twins in the first trimester and adverse outcomes.^{8–10} However, the strength of CRL discordance as a predictor of adverse outcomes has been questioned.¹¹

The aim of this study was to evaluate the outcome in DCDA twin pregnancies conceived by IVF according to CRL

discordance at 11–14 weeks primarily of fetal loss less than 24 weeks and PTB before 32 weeks' gestation, in an attempt to assess the usefulness of CRL discordance as a predictor of adverse outcomes.

MATERIALS AND METHODS

Study Design

This was a prospective observational cohort study conducted over a period of 1 year from October 2021 to September 2022.

Patient Selection

All antenatal patients who were conceived with IVF in our hospital and with live DCDA twin gestation were enrolled in the study at 11–14 weeks. Exclusion criteria were DCDA twins with one vanishing twin, heterotopic pregnancies, referred cases after the first trimester, and lost to follow-up cases.

Antenatal ultrasound was performed using Voluson-E6 and E8 machines using curvilinear probes with the frequency of 3.5–5 MHz by Fetal Medicine Foundation (FMF)-certified consultants. The pregnancy was dated by the date of embryo transfer *in vitro* fertilization. Dichorionic twin pregnancies with CRL between 45 and 84 mm were included in the study. A detailed structural survey was performed for each co-twin to rule out anatomical abnormalities. Crown–rump length was measured with the fetuses in a neutral position and a magnification such that the fetus occupies most of the screen and by an average of three measurements as per the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations.¹²

The CRL discordancy (%) was calculated using the formula:

$$\frac{[(\text{CRL of larger twin} - \text{CRL of smaller twin}) / \text{CRL of larger twin}] \times 100}{}$$

The fetuses were classified into two groups based on the presence of significant CRL discrepancy of more than or equal to 10% into the discordant and concordant groups. All those twin gestations enrolled in our study were followed up with clinical and ultrasound examinations as per ISUOG recommendations.¹² Detailed anatomical survey was carried out to rule out structural abnormalities around 18–22 weeks followed by ultrasound 4 weekly for biometry and Doppler. On each visit, fetal biometry was performed and an estimated fetal weight discrepancy between the twins was noted. Also, FGR, and selective FGR were classified as per Delphi consensus.¹³ Surveillance frequency was adjusted based on the staging of intrauterine growth restriction (IUGR) in those twins. The two groups (discordant and concordant) were followed up to assess for pregnancy and perinatal outcome measures. Delivery was planned in between 37–38 weeks in uncomplicated twins and depending on the stage of FGR or other obstetric complications in complicated pregnancies. These babies were followed up over a period of 28 days.

Outcomes

The primary outcome measures were single fetal losses or pregnancy loss below 24 weeks, and PTB below 32 weeks. The secondary outcome measures were structural abnormalities, FGR in one or both twins, preeclampsia, the fetal demise of 1 or both fetuses after 24 weeks, mean gestational age (GA) at the delivery, mean birth weight (BW), BW discordancy above 20% between twins, perinatal outcomes (NICU stay > 7 days, neonatal deaths).

Statistical Analysis

The categorical and quantitative variables were expressed as frequency (percentage) and mean \pm SD, respectively. The Chi-square test and Fisher's exact test were used to find the association between categorical variables. For all statistical interpretations, $p < 0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical package for the social sciences (SPSS) software, version 20.0.

RESULTS

A total of 188 women with live DCDA pregnancies were enrolled in the study, among those 188 women, 12 women were lost to follow-up and hence the results were analyzed in 176 women.

Among 176 women, 53 were in the discordant group (30%) and 123 were in the concordant group (70%). The results are summarized in Table 1.

Primary outcome measures of total pregnancy loss of below 24 weeks and PTB below 32 weeks occurred 2 times more commonly in the discordant group compared to the concordant group (23% vs 9%, $p = 0.013$; 24.5% vs 12%, $p = 0.04$, respectively). The secondary outcome measures such as discordant structural abnormalities, selective FGR, and BW discordance were significantly more in the discordant group compared to the concordant group (10% vs 2%, $p = 0.04$; 58% vs 32% $p < 0.01$; 68% vs 32% $p < 0.01$). Mean GA at delivery and mean BW was significantly low in the discordant group. The NICU stay for more than 7 days was significantly more in the discordant group. There was no significant difference in stillbirths or neonatal death in the study groups.

DISCUSSION

The incidence of CRL discordance (30%) is high compared to that reported in the literature and this might be due to IVF conceptions and a high proportion of women with advanced maternal age compared to other studies. A total of 51% of the women included in the study were above 30 years and 30% were above 35 years. The study groups were similar with respect to age, body mass index (BMI), parity, IVF procedure, culture day, and the number of embryos transferred.

Total pregnancy loss below 24 weeks due to spontaneous miscarriage occurred in 12 women (23%) in the discordant group and in 11 women (9%) in the concordant group. Pregnancy loss of less than 24 weeks was seen in 3 out of 6 cases (50%) with severe CRL discrepancy of above 15%. Pregnancy loss before fetal viability was twice as common in the discordant group compared to the concordant group, there is a statistically significant association between pregnancy loss before 24 weeks and CRL discrepancy and the risk increases with the severity of discordance. Our results are comparable to the studies conducted by Harper et al.¹⁴ and Grande et al.¹⁵

Single fetal demise was seen at 20 weeks in 2 women in the discordant group and 1 woman in the concordant group. One of the single fetal losses in the discordant group was due to early onset selective FGR stage II at 20 weeks and single fetal demise at 24 weeks. Also, 1 each in both groups had a single fetal demise detected at 20 weeks during an anomaly scan with no known cause. Both pregnancies resulted in the delivery of a single live fetus at 37 weeks. So, there was no statistical difference in the groups for single fetal loss below 24 weeks.

Discordant structural abnormalities were seen in 5 women (10%) in the discordant group and 3 women (2%) in the concordant

Table 1: Perinatal outcome measures in study groups

Outcome	Discordant group		Concordant group		p-value
	N	%	N	%	
Fetal loss <24 weeks					
Single fetus	1	2	1	1	0.5
Both fetuses	12	23	11	9	0.013
Structural abnormalities	5	10	3	2	0.04
FGR					
Selective FGR	30	58	17	32	<0.01
Both fetuses	6	12	12	10	0.7
PTB	13	24	15	12	0.04
Preeclampsia (PE)	8	15	12	10	0.3
Fetal demise					
Single fetus	1		0		NA
Both fetuses	0		0		NA
GA at delivery – mean (SD)	34.4 (2.6)		35.2 (1.2)		0.01
BW – mean (SD)	2350 (660)		2780 (310)		<0.01
BW discordance	36	68	17	32	<0.01
NICU stay (>7 days)	15	28	18	15	0.03
Neonatal death	2	4	2	1.6	0.76

NA, not applicable; SD, standard deviation

group. Structural abnormalities observed in the study were trisomy 21, congenital talipes equinovarus, anencephaly, ventricular septal defect, tetralogy of fallot, bilateral ventriculomegaly, omphalocele, diaphragmatic hernia. All the anomalies were in smaller twins in the discordant group. The selective fetal reduction was done in two cases with anencephaly and omphalocele. There were no preterm deliveries in any of the pregnancies with structural abnormalities. Pregnancies with selective fetal reduction resulted in the term delivery of a single live fetus. In our study, a statistically significant association between CRL discrepancy and structural abnormalities was present. Our study results are comparable to the study by Grande et al.,¹⁵ where chromosomal abnormalities (9.2 vs 0.9%) and structural anomalies (14 vs 2.6%) were more frequent in discordant than in concordant twins.

The PTB before 32 weeks included both spontaneous PTB and induced PTB. The PTB was 2-fold more common in CRL discordant group (13 cases: 24%) as compared to the concordant group (15 cases: 12%). The PTB was spontaneous in 7 cases and induced in 5 cases of the discordant group. Our results are comparable with Johansen et al. which also showed a statistically significant association between CRL discrepancy and PTB. However, the main cause of the increased incidence of PTB in our study is FGR.

Selective FGR was significantly more in the discordant group (30 cases: 58%) than in the concordant group (17 cases: 32%). Selective FGR occurred in 3 out of 6 cases (50%) in CRL discrepancy with more than 15% which is similar to the proportion seen with a discrepancy of above 10%. Also, FGR of both fetuses occurred in 6 cases (12%) in the discordant group and 12 cases (10%) in the concordant group, and the difference is not statistically significant. Single fetal demise occurred in 1 fetus in the discordant group at 28 weeks with selective FGR stage III and none in the concordant group. There were no intrauterine deaths of both fetuses in either group. Preeclampsia is seen more commonly in 8 cases (15%) in the

discordant group and 12 cases (10%) in the concordant group but the difference is not statistically significant. Significant BW discordance ($\geq 20\%$) was observed in 36 cases (68%) in discordant twins and 17 cases (32%) in concordant twins. Among the discordant group, most of the twins (32%) showed a BW discordance of 20–24%. Statistically significant BW discordance was observed in the discordant group as compared to the concordant group, which is comparable to the studies conducted by Grande et al.¹⁵ and D’Antonio F et al.¹¹ The maximum BW discordance was 52% and the twin showed a CRL discordance of 16%.

Mean GA at delivery and mean BW was significantly low in the discordant group compared to the concordant group (34.4 weeks vs 35.2 weeks, 2350 gm vs 2780 gm, $p < 0.05$). The NICU stay above 7 days was seen in 15 neonates in the discordant group and 17 neonates in the concordant group. Neonatal admissions were twice more likely in the discordant group mainly for preterm care as PTB was more common in the discordant group. Neonatal death was seen in 2 neonates in each group and all 4 deaths were due to extreme PTB below 28 weeks. There was no statistically significant correlation between CRL discrepancy and neonatal death. These pregnancy complications like fetal loss below 24 weeks, structural anomalies, PTB, FGR, growth discordance, preeclampsia, LBW, NICU stay, and neonatal deaths due to PTB were more common in our study compared to other studies on CRL discordant pregnancies as the study was in DCDA pregnancies conceived by IVF which is an additional risk factor for these complications. The limitations of this study are its smaller sample size and lack of long-term follow-up of these discordant twins.

CONCLUSION

This study shows that divergent growth patterns may begin early in pregnancy and are detectable by ultrasound by 11–14

weeks. This study on 176 dichorionic gestations conceived by IVF demonstrated a statistically significant association between CRL discrepancy and adverse outcomes such as pregnancy loss below 24 weeks, discordant structural abnormalities, selective FGR, PTB below 32 weeks, BW discordance, and NICU admissions. These complications are higher than the reported incidence of the complications in DCDA twins conceived by non-ART methods as IVF is an independent risk factor for these adverse pregnancy outcomes. An early detection of discordant twin growth in these IVF pregnancies helps us to follow up on these pregnancies more closely for timely decision making.

However, this should be weighed against the anxiety and potentially unnecessary concern caused by the finding of CRL discordance. In addition, in women with comorbid medical conditions like cardiac disease, renal disease, history of PTB, current discordant twins would be an additional risk factor for adverse pregnancy outcome for PTB and hence selective fetal reduction of the smaller twin may be considered. However, in this study, no adverse perinatal outcomes apart from PTB due to selective FGR, and discordant BW were observed in continuing pregnancies, and it is not strongly suggested that a fetal reduction operation be undertaken at the first scan.

Clinical Significance

First-trimester determination of chorionicity is vital for planning antenatal visits and further management of gestation. Significant CRL discrepancy in the first trimester will help us to identify the high-risk group. An additional USG at 16–18 weeks for early detection of structural anomalies and early onset FGR due to genetic causes should be recommended in the discordant group. This will help in buying some time for genetic studies and also in reducing the complications of pregnancy loss due to selective fetal reduction at higher gestational age. After excluding anomalies, CRL discordant twins are then to be followed with monthly growth assessment and Doppler studies to enable early detection of selective FGR.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

Geeta Devi G has contributed to the concept design of the article, acquisition, and analysis of the data. Ruchi Hooda has made a substantial contribution to the acquisition, analysis, and interpretation of data for the article.

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