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Intertwin discordance in MCA-PI and CPR in the prediction of TTTS progression

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Objective

Twin-to-twin transfusion syndrome (TTTS) is the commonest and most severe complication to occur specific to monochorionicity. The role of standardised fetal surveillance and timely institution of fetal therapy cannot be over-emphasized for optimal outcomes in pregnancies complicated with TTTS. In the current scenario, surveillance for development of TTTS is recommended every fort-nightly from 16 weeks onwards. In addition, intensive surveillance is warranted in TTTS-affected cases to study the progression of disease (upstaging) and to detect the development of super-imposed complications such as single intra-uterine demise (sIUD)/double intra-uterine demise (dIUD) and/or selective fetal growth restriction (sFGR), double fetal growth restriction (dFGR). However, the literature assessing the parameters for early detection of TTTS and for prediction of disease progression with or without super-imposed complications is sparse. The purpose of this study was to investigate the role of inter-twin discordance of Middle Cerebral Artery Doppler PI (MCA-PI) and Cerebro-Placental Ratio (CPR) in prediction of “net complications” that included either onset of TTTS, progression of TTTS, and development of sFGR or dFGR.

Methods

This is a retrospective study of prospectively collected data from a tertiary fetal care centre in South India. The study period was from January 2010 to December 2021. All pregnancies had confirmed dating and chorionicity at the first trimester scan. The study of fetal biometry, liquor and Doppler was done at every visit by FMF certified operators, and the data was recorded on Astraia fetal database software. All euploid, structurally normal monochorionic diamniotic pregnancies with both twins alive at the first examination were studied for the development of monochorionic complications. TTTS was diagnosed if there was a discrepancy in the amniotic fluid of more than 8 cm in the recipient sac and less than 2 cm in the donor sac. TTTS was staged as per Quintero staging. Pregnancies that developed TAPS were excluded. In pregnancies that developed TTTS-Quintero stage 2 and above, Fetoscopic Laser Ablation (FLA) was offered. Hence, these pregnancies were excluded for the purpose of development of “superimposed complications” after performing FLA. On the other hand, some couple chose against any intervention. These were included in the study as this formed a part of the natural progression of the disease. The study of fetal Doppler included assessment of Umbilical Artery PI (UA-PI), Middle Cerebral Artery PI (MCA-PI) and Ductus Venosus PI (DV-PI) using the techniques of acquisition as per FMF guidelines. Cerebro-placental ratio (CPR) was calculated by dividing UA-PI with MCA-PI. Discrepancy in MCA-PI and CPR, was calculated as percentage discrepancy of the “higher” value. A discrepancy of 20% or more between the two fetuses was considered to be “discordant” for the purpose of this study. Pregnancy outcomes were obtained by telephonic/electronic communication with the parents and assessment of delivery details from hospital records.

Results

107 pregnancies were included in the study, of which 25/107 (23.3%) had TTTS as the primary complication. 82 (76.7%) pregnancies had no TTTS and were considered as controls. Data was available for “time interval” i. e. , onset of discordancy to onset of incident, defined as onset of TTTS, disease progression as per Quintero staging and development of additional complication in the 25 TTTS-affected pregnancies. There were 28 “net complications” which included 10/28 (35.8%) onset of TTTS, 9/28 (32.1%) of disease progression and 9/28 (32.1%) with development of additional complication, in particular fetal growth restriction of one or both babies. dMCA was present in 19/28 (67.8%) observations when any one of the “net complications” occurred. dMCA was seen in 34/82 (41.4%) observations, in the absence of any complication. In the pregnancies that had onset of TTTS, dMCA was first present in 5/10 (50%) observations and preceded its development by 1-8 weeks. In the pregnancies with disease progression, 8/9 (88.9%) had first dMCA, 1-4 weeks in advance. In pregnancies that had superimposed FGR, 6/9 (66.7%) had first dMCA, 1 – 12 weeks in advance. The sensitivity and specificity of dMCA of more than or equal to 20% in detection of any complication, progression or superimposed complication was 67.8% and 58.5% respectively. The negative predictive value was 84.2%. The OR was 2.98 (95% CI- 1.20-7.37, $p<0.01$) for risk of developing/worsening TTTS. dCPR was present in 21/28 (75.0%) observations when any of the “net complications” occurred. dCPR was seen in 44/82 (53.6%) observations, in the absence of any complication. In the pregnancies with onset of TTTS, dCPR first presented in 6/10 (60%) observations and preceded its development 1-8 weeks. In the pregnancies with disease progression, all observations 9/9 (100%) had first dCPR, 1-4 weeks in advance. In pregnancies that had superimposed FGR, 6/9 (66.7%) had first dCPR, 1-12 weeks in advance. The sensitivity and specificity of dCPR of more than or equal to 20% in detection of any complication, progression or superimposed complication was 75.0% and 46.3% respectively. The negative predictive value was 84.4%. The OR was 2.59 (95% CI- 0.99-6.76, $p<0.051$, NS) for risk of developing/worsening TTTS.

Conclusion

Our study attempted to assess inter-twin discordance in Middle Cerebral Artery PI and Cerebro- Placental Ratio as a novel approach to predict the onset of TTTS, disease progression and development of super-imposed FGR. The study suggests that dMCA and dCPR can precede the development of any of the complications. The risk for development or worsening of TTTS, nearly tripled if the dMCA was present in the preceding examinations. In our study this discordance could be seen as early as 16 weeks, up to 32 weeks. This finding could add further value to enhance surveillance in monochorionic twin pregnancies by earlier prediction of potential complications, thereby allowing early and timely referral of these pregnancies. The role of dCPR in prediction or worsening of TTTS could not be ascertained as the results were statistically insignificant. This could best be attributed to the unavailability of data, for time interval of onset of TTTS or its subsequent worsening skewed by more referrals to our set-up. We recommend testing this hypothesis in larger cohort and the assessing the benefit of early prediction for timely referral and or intervention to improve the postnatal outcomes.

Table 1 : Patient characteristics with complications

Diagnosis with "Net complications"	Number of Complications	GA of development of complication (in weeks)	Interval from discordance to complication (in weeks)
sFGR 3/TTTS 4 -> sIUD	1	26	3
TTTS 1 -> sFGR 1	1	28	3
TTTS 1 -> dFGR	1	29	4
TTTS 4	1	26	8
TTTS 1, TTTS 1 -> sFGR	2	18, 20	2, 4
TTTS 3 -> sIUD	1	18	2
TTTS 1	1	31	4
TTTS 3 -> dMA	1	17	1
TTTS 4 -> sIUD	1	33	1
TTTS 1 -> sFGR 1	1	23	4
TTTS 1-> TTTS 3	1	20	2
TTTS Q1-> Q 3, Q1 -> sFGR -1	2	21, 21	4, 4
TTTS 2	1	17	1
TTTS 3 -> dFGR	1	32	10
TTTS 1, TTTS 1-> dMA	2	18, 19	2, 3
TTTS 2 -> sFGR 3	1	24	1
TTTS 1-> sFGR 1	1	24	4
TTTS 1	1	23	2
TTTS 1	1	21	2
TTTS 1	1	25	1
TTTS 3 -> sFGR 2	1	17	1
TTTS 1	1	24	8
TTTS 1	1	21	1
TTTS 3/sFGR -> dMA	1	21	1
TTTS 3 -> dMA	1	22	1

Keywords *: TTTS – Twin-to-twin Transfusion Syndrome, sFGR/dFGR - selective fetal growth restriction/ fetal growth restriction in both, sIUD/dIUD – single intra-uterine demise/ double intra-uterine demise, dMA – Missed abortion in both*

Table 2 : Breakup of "net complications" for dMCA and dCPR with time interval

Variable	Onset of TTTS (10)	Progression of disease (9)	Development of additional complications (9)
dMCA + =19/28	5/10 ; 1-8 weeks	8/9 ; 1-4 weeks	6/9 ; 1-12 weeks
dCPR + =21/28	6/10 ; 1-8 weeks	9/9 ; 1-4 weeks	6/9 ; 1-12 weeks

Table 3 : Statistical analysis for dMCA and dCPR in predicting any of the "net complications"

Variable	Sensitivity	Specificity	Odds Ratio (OR)
dMCA +	67.8%	58.5%	2.98 (95% CI- 1.20-7.37, p<0.01)
dCPR +	75.0%	46.3%	2.59 (95% CI- 0.99-6.76, p<0.051)