ORIGINAL RESEARCH

Sonographic Umbilical Cord Parameters in Third Trimester of Pregnancy with Gestational Diabetes Mellitus as Predictors of Macrosomia

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Abstract

Background: Gestational diabetes mellitus (GDM) is associated with various complications. Macrosomia is one such complication.

Aim: To predict fetal macrosomia by sonographic measurements of umbilical cord thickness (CT) and cross-sectional area (CSA) in GDM in third-trimester.

Method: This prospective-cohort-observational study on 40 antenatal women with GDM (group I) over a period of 12 months at a tertiary teaching institute against 40 antenatal women without GDM or any medical co-morbidity (group II). Cord parameters [CT (cm) and CSA (cm^2)] were assessed sonographically after 36 weeks. Pregnancy outcomes were noted. CT/CSA value more than 90th centile taken as cut-off value was considered as large cord. The predictive accuracy of the cut-off of cord parameters to predict macrosomia was calculated.

Results: The mean age and BMI of women under study were 27.9 ± 2.84 years and 26.05 ± 1.32 kg/m^2. The cut-off of large cords was 2.8 cm and 3.56 cm^2 for CT and CSA, respectively. Large cords were found in 70% of the study group. Sonographically detected umbilical-cord parameters were significantly larger in macrosomic fetuses as compared to nonmacrosomic fetuses macrosomia was found in 17.5% cases of study group. The sensitivity, specificity, positive predictive value, and negative predictive value of cord parameters to predict macrosomia were 57.1, 96.9, 80, and 91.4% for CT and 65.7, 63.6, 46.2, and 87.5% for CSA, respectively.

Conclusion: Sonographically detected umbilical CT and CSA are good predictors of fetal macrosomia with high negative predictive value.

Clinical significance: Cord is an easily accessible and assessable organ requiring minimal expertise for sonographic assessment compared to other available parameters. Thus, it can be used as an easy option to predict macrosomia along with other predictors.

Keywords: Adverse perinatal outcome, Body mass index, Shoulder dystocia prediction, Third trimester, Third trimester scan, Ultrasonography, Umbilical cord.

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Introduction

The umbilical cord is a vital structure between placenta and fetus which can provide wide information about growing fetus. The cord thickness is proportionate to the amount of Wharton's jelly (WJ) present in the cord. As a mucous connective tissue, it is rich in proteoglycans providing protection and insulation to the cord. Umbilical cord thickness has been related to birth weight in previous studies.[1–3] Most of the studies have been anatomical done in the postpartum period.[4,5] As per the existing guidelines, the sonographic assessment of the cord has been restricted to Doppler evaluation and number of vessels [International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) Guidelines].[5] Extension of ultrasonography can be done for the assessment of other cord parameters like thickness and CSA.

Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy. Fifteen to forty five percent of babies of diabetic mothers have macrosomia. The risk is three times higher than in normoglycemic controls.[6] Macrosomia is defined as birth weight more than 90th percentile or more than two standard deviations for the gestational age or more than 4000 gm. Macrosomic fetuses are at risk for complications like premature birth, shoulder dystocia, obstructed labor, brachial plexus injury, skeletal injuries, neonatal hypoglycemia, dyselectrolytemia, Meconium aspiration syndrome, neonatal jaundice, etc.[7,8] The mortality and morbidity are more in macrosomic fetuses compared with normal weight fetuses.[9] Even the mother of macrosomic fetuses is at risk of complications like operative delivery, third and fourth degree perineal lacerations, postpartum infection, and hemorrhage.[10]

Timely and accurate prediction of this condition is therefore important to prevent all these complications. There have been many parameters. The macrosomic fetus has more marked development of this subcutaneous fat, particularly in cases with GDM. Conventionally effective fetal weight (EFW) had been

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estimated using biometric parameters most frequently being bi-parietal diameter (BPD), abdominal circumference (AC), and femur length (FL).[11] Ultrasound-based birth weight prediction has been done using different methods like fat thickness assessment at various locations but it has not been comparable to conventional biometry.[12] All these parameters are technically difficult, time-consuming, and need a certain level of expertise. Cord is an easily measureable and reachable organ through sonography. However, the association between change in cord parameters and fetal outcomes has not been fully established in the literature. There is paucity of Indian literature in this respect.

With this background, this study was designed to study the role of sonographically determined cord parameters for the prediction of fetal macrosomia in women with gestational diabetes. This can provide important prognostic information about the fetal outcome, and thus, adverse outcomes may be obviated by well-planned delivery.

Materials and Methods

This was an observational prospective case-control study done in the Department of Obstetrics and Gynaecology at a Tertiary Teaching Institute, from October 2017 to September 2018. It was conducted on 40 antenatal women with GDM in third trimester (≥36 weeks) constituting the study group I against the control group II comprising 40 antenatal women without GDM without any feto-maternal comorbidity. Inclusion criteria consisted of single live intrauterine fetus with normal amniotic fluid index (8–24) with three vessel unit umbilical cord in late third trimester of pregnancy (≥36 weeks of gestation). The cases with any clinical/ultrasonographic signs of fetal growth restriction (FGR), multiple gestation, fetal congenital malformation, pregnancy with medical disorders like overt diabetes, hypertension, renal disease, heart disease, anemia, hypothyroidism, etc., were excluded. Gestational diabetes mellitus was diagnosed in these women after universal screening of all antenatal women at first contact or at 24–28 weeks as per Government of India recommendation using 2 hours oral glucose tolerance test with 75 gm of glucose and a cut-off value of 140 mg/dL [Diabetes in Pregnancy Study Group of India (DIPSI)].[13] After informed consent, recruitment was done as per inclusion criteria.

Gestational age was calculated from the first day of the last menstrual period (LMP) and confirmed by first trimester ultrasound. Body Mass Index (BMI) of the women was calculated using the formula: BMI = Pre-pregnancy weight (kg)/Height (m^2) and classified according to the WHO classification for Asian population. All ultrasonography examinations were done by single observer (to abolish the interobserver bias) blinded to clinical features of women under study, with standard USG scanner (Philips Healthcare Unit, Philips HD11 XE) using a 5 MHz curvilinear probe. After placing the probe over the abdomen, CT sonographic measurements were taken digitally by marking the outer edges of the umbilical cord in free floating loop which was noted in centimeters up to smallest millimeter (Fig. 1). For CSA, outer edge of the same loop of cord was encircled in transverse section and the value given by the software was noted in centimeter square (Fig. 2). Lean umbilical cord was considered as lean if CT/CSA value was below 10th percentile. Large umbilical cord was considered thick when it was above 90th percentile. (10th and 90th centiles were calculated for each parameter after plotting the reading on ROC using the data collected in our study).

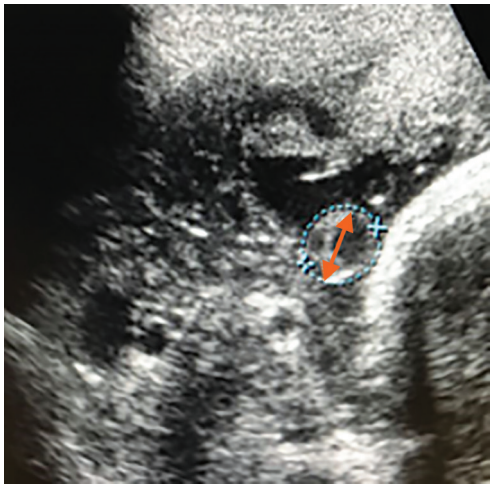

Fig. 1: Sonographic estimation of cord thickness

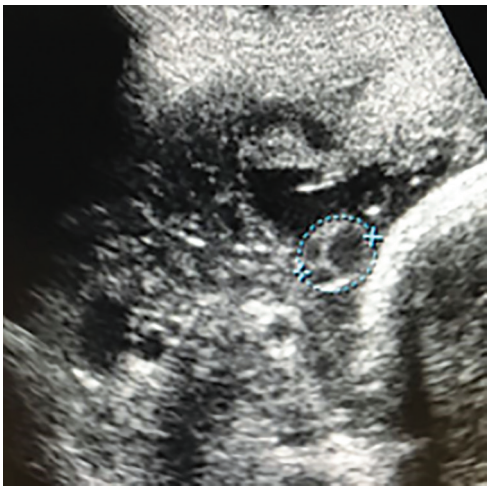

Fig. 2: Sonographic estimation of cord cross-sectional area

All the cases were followed till delivery in terms of parameters like cardiotocographic findings, period of gestation at the time of delivery, meconium stained liquor, mode of delivery, birth weight, sex of the baby, and APGAR score. Birth weight was measured with Seca 725 mechanical baby weighing scale (Seca Co. Ltd USA) calibrated in grams when infant was naked. Low birth weight and macrosomia were considered for weight <2500 gm and >4 kg, respectively, at birth. Meconium staining of amniotic fluid was considered by intrapartum assessment of amniotic fluid. APGAR was considered low at score less than 7 at 5 minutes. The physical CT was measured in immediate postpartum period using Vernier Calipers.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then nonparametric test was used. Statistical tests were applied as follows:

- Quantitative variables were compared using Independent *t* test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups.

- Qualitative variables were correlated using Chi-square test/ Fisher's exact test.
- Receiver operating characteristic curve was used to find out cut-off point of parameters for predicting macrosomia.

Centiles were calculated for each parameter; accordingly cord thickness and area classified as large. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of umbilical cord thickness and area were calculated.

A *p*-value of <0.05 was considered statistically significant.

The data were entered in the MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Data were compiled for 80 women under study and control group. Of 40 women in study group with GDM, 65% (26) women had GDM with medical nutrition therapy (MNT), 20% (8) had GDM on insulin while 15% (4) had GDM and were on oral hypoglycemic agents. Table 1 shows the clinical profile of both groups. Although both groups were similar in context of age, previous history of GDM, or family history DM, yet there was a significant difference in terms of BMI which was more in study group I. Of the seven babies who had macrosomia, high BMI (>26) was found in 28.5% (2) mothers.

Table 2 shows that both sonographic and anatomical mean cord thickness and cord cross-sectional area were significantly higher in study group I than in control group II. Moreover no significant difference was found between sonographic and anatomical cord thickness ($p > 0.001$). Materno-fetal parameters like cardiotocographic findings, mean period of gestation at delivery, meconium stained liquor, mode of delivery, sex and APGAR score (at 5 minutes) were similar in the two groups. However, the birth weight was significantly more in group I. Macrosomia (>4 kg) was found in 17.5% babies in group I in comparison with none in group II. A significant positive correlation was found between umbilical cord parameters and birth weight in a linear trend with mean as 3.47 kg from a range of 3–4.35 kg in GDM ($p < 0.001$).

As depicted in Table 3, the cut-off, i.e., 95th centile, of the cord parameters were 2.8 cm and 3.56 cm^2 for CT and CSA, respectively. Accordingly, large cord was found in 70% of group I with GDM. Seventeen point five percent of this group had macrosomia compared to none in group II. All babies with macrosomia had sonographic large cord.

Table 4 shows that sensitivity, specificity, positive predictive value, and negative predictive values were 57.4, 96.9, 80, and 91.4%, respectively, for CT and 65.7, 78.8, 46.2, and 96.4%, respectively, for CSA. While the same for maternal BMI as predictor of macrosomia was 57.14, 63.6, 25, and 87.5%, respectively.

Discussion

Diabetes has been seen to complicate 7% of all pregnancies and 86% of these cases are due to GDM.[14] The results of the hyperglycemia and adverse pregnancy outcome study (HAPO), an international, multicentric study, established definite relationship between maternal glycemic levels and fetal complications like cesarean section, birth weight greater than the 90th percentile, neonatal hypoglycemia, and fetal hyperinsulinemia.[15] The persistent maternal hyperglycemia leads to fetal hyperglycemia and insulin-like growth factor release thereby causing macrosomia. Macrosomic babies have high odds of labor abnormalities, shoulder dystocia, birth trauma, and permanent injury to the neonate.[16] Thus prediction of birth weight is very prudent in order to avoid these complications, by planning timely decisions and hence better management.

Umbilical cord remains an easily accessible and assessable organ to predict birth weight in precise way in very less time. Conventional biometry takes much longer and needs a learning curve. Previous studies have shown that cord area and thickness increase with gestational age till 32–34 weeks in uncomplicated pregnancy and then later plateaus in normal gestation.[17,18]

In the present study, large cord parameters have been seen in fetus of women with GDM in comparison to those without GDM. The possible mechanism may be endothelial damage in cord vessels making them leaky for plasma proteins leading to increase in WJ's volume. Similar results were cited by Weissman et al. and Cromi

Table 1: Clinical profile of the women under study

Clinical profile	*Group I N = 40 (%)*	*Group II N = 40 (%)*	*Total N = 80*	*p-value*
Age (years)				0.005 (NS)
21–25	7 (17.50%)	4 (10%)	11 (13.75%)	
26–30	25 (62.50%)	36 (90%)	61 (76.25%)	
>30	8 (20%)	0 (0%)	8 (10%)	
Mean age (years)	27.9 ± 2.84	27.78 ± 1.94		
Previous history of GDM				0.005 (NS)
No	40 (100%)	32 (80%)	72 (90%)	
Yes	0 (0%)	8 (20%)	8 (10%)	
Family history				0.026 (NS)
No	40 (100%)	34 (85%)	74 (92.50%)	
Yes	0 (0%)	6 (15%)	6 (7.50%)	
BMI (kg/m^2)				<0.001 (S)
21–25	7 (17.5%)	10 (25%)	17	
25–30	11 (27.5%)	22 (55%)	33	
>30	22 (55%)	8 (20%)	30	
Mean BMI	26.05 ± 1.32	24.02 ± 1.39		

BMI, body mass index; NS, nonsignificant; S, significant

Table 2: Cord parameters and materno-fetal outcomes in study group I and control group II

Cord parameters	*Group I (N = 40)*	*Group II (N = 40)*		*p-value*
Cord thickness (CT) cm				<0.0001 (S)
Mean ± SD	2.73 ± 0.14	1.7 ± 0.37		
Median	2.76	1.8		
Min-Max	2.45–2.97	0.9–2.28		
Interquartile range	2.610–2.810	1.375–1.960		
Cord cross-sectional area (CSA) cm^2				<0.0001 (S)
Mean ± SD	3.48 ± 0.23	2.15 ± 0.51		
Median	3.54	2.22		
Min-Max	3.02–3.91	0.93–2.84		
Interquartile range	3.270–3.610	1.75–2.55		
Materno-fetal parameters	*N (%)*	*N (%)*	*Total*	*p-value*
Cardiotocographic finding				
Reactive	40 (100%)	40 (100%)	80 (100%)	1.4 (NS)
Mean period of gestation at delivery (weeks)	38.5 ± 0.78	38.5 ± 0.96		0.764 (NS)
Meconium stained liquor				
No	34 (85.00%)	34 (85.00%)	68 (85.00%)	1.000 (NS)
Yes	6 (15.00%)	6 (15.00%)	12 (15.00%)	
Mode of delivery				
Cesarean	20 (50.00%)	5 (12.50%)	25 (31.25%)	0.0003 (NS)
Normal vaginal	20 (50.00%)	35 (87.50%)	55 (68.75%)	
Birth weight (kg)				
<2.5 kg	0 (0.00%)	16 (40.00%)	16 (20.00%)	<0.0001 (S)
2.5–4 kg	33 (82.50%)	24 (60.00%)	57 (71.25%)	
>4 kg	7 (17.50%)	0 (0.00%)	7 (8.75%)	
Mean birth weight (kg)	3.47 ± 0.37	2.54 ± 0.3		
Apgar (5 minute)	7.32 ± 0.73	7.25 ± 1.03		0.906 (NS)
Sex				
Female	21 (52.50%)	18 (45.00%)	39 (48.75%)	0.502 (NS)
Male	19 (47.50%)	22 (55.00%)	41 (51.25%)	
Total	40 (100.00%)	40 (100.00%)	80 (100.00%)	
Mean anatomical cord thickness (cm)	2.71 ± 0.12	1.7 ± 0.08		<0.0001 (S)
p-value (compared to value in respective group)	>0.001 (NS)	>0.001 (NS)		

NS, non significant; S, significant; No statistical significant difference found between sonographic CT and anatomical CT

Table 3: Distribution of large cord, i.e., (CT >2.8 cm; CSA >3.56 cm^2) and macrosomia in study and control group

Parameters		*Group I (N = 40)*	*Group II (N = 40)*	*Total (N = 80)*	*p-value*
Large cord					
CT >2.8 cm	No	12 (30%)	40 (100%)	52 (65%)	<0.0001 (S)
CSA >3.56 cm^2	Yes	28 (70%)	0	28 (35%)	
Macrosomia	No	33 (82.50%)	40 (100%)	73 (91.25%)	0.012 (NS)
	Yes	7 (17.50%)	0 (0%)	7 (8.75%)	

CSA, cross-sectional area; CT, cord thickness; NS, non significant; S, significant

et al.[19,20] Ghezzi et al. also demonstrated that macrosomic infants of diabetic mothers had a large umbilical cord.[9] Increase in Wharton jelly content has been suggested as the main cause of increase in the cord width.[19] Significant rise in cord parameter in late third trimester in pregnancy with GDM has also been demonstrated.[21] Moreover, Cromi et al. have suggested an interesting finding. If a large cord has been detected on ultrasound, assessing the relative contribution of WJ jelly area and area of umbilical vessels to overall cross-sectional area can help in differentiating constitutionally big fetus from macrosomic fetus due to maternal diabetes. The endothelial damage in cord vessels explains this in diabetic mother while this will be absent in constitutionally large baby.

The anatomical and sonographic cord parameters were similar with no significant statistical difference which again reiterates that ultrasonography should be utilized in antepartum period to predict macrosomia (Table 2).

The present study demonstrated 17.5% macrosomia in study group. Naylor et al. have reported macrosomia in 16–29% of patients with GDM. The relative risk of macrosomia varies between 1.5 and 3 times higher in the diabetic population.[22]

Table 4: Sensitivity, specificity, positive predictive value and negative predictive value of cord parameters and BMI for predicting macrosomia

Parameter	*AUC*	*Standard error*	*95% confidence interval (CI)*	*p-value*	*Cut-off*	*Sensitivity*	*95%CI*	*Specificity*	*05%CI*	*PPV*	*95%CI*	*NPV*	*95%CI*
CT (cm)	0.784	0.12	0.625–0.898	0.0184	>2.88	57.14	18.4–90.1	96.97	84.2–99.9	80	28.4–99.5	91.4	76.9–98.2
CSA (cm^2)	0.825	0.112	0.672–0.926	0.0037	>3.5	65.7	42.1–99.6	78.79	61.1–91	46.2	19.2–74.9	96.3	81–99.9
BMI (kg/m^2)	0.565	0.155	0.399–0.721	0.676	>26	57.14	18.4–90.1	63.64	45.1–79.6	25	7.3–52.4	87.5	67.6–97.3

AUC, area under curve; BMI, body mass index; CI, confidence interval; CSA, cross-sectional area; CT, cord thickness; NPV, negative predictive value; PPV, positive predictive value; SE, standard error

In the context of maternal BMI, BMI >26 had sensitivity and specificity of 57.1 and 63.64%, respectively, with a low positive predictive value of 25% but a high negative predictive value of 87.5% implying that if maternal BMI is not high, possibility of macrosomia also remains low.

In the present study, umbilical cord parameters have good specificity and high negative predictive value (Table 4). Hence, if umbilical cord thickness and area remain less than 90th centile, the chance of macrosomia is less. Similar results were given by Janani et al.[23]

Strength and Limitations

The biggest strength of this study is the use of an easily assessable and reachable sonographic parameter for prediction of fetal macrosomia. This assessment needs a little training in comparison to fetal biometry which requires expertise. It is less time-consuming than conventional biometry. Thus, it can be utilized as one of the predictors of macrosomia in maternal GDM. The limitation is that cord parameters have been studied alone in the present study. The predictive accuracy of sonographic cord parameters can be tested by using it along with conventional biometry for detecting macrosomia. Thus, further studies can be planned on these lines.

Conclusion and Clinical Significance

There exists a significant association of sonographic umbilical cord thickness and cross-sectional area in late third trimester of pregnancy with GDM with macrosomia. Having a high negative predictive value, the cord parameters can be made a part of routine antenatal third trimester ultrasound along with other predictors for prediction of macrosomia in women with GDM and with high BMI. Being technically easy to be done on an approachable fetal organ, i.e., umbilical cord, it can be used in peripheral areas to predict macrosomia *in utero* and should prompt well-timed transfer to a tertiary center for optimum materno-fetal outcome.

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