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Critical evaluation of umbilical cord morphometry in pregnancies with normal and abnormal glucose metabolism: An ultrasound based study

Sapna Amin, Shripad Hebbar, Deepika Pothakamuri and Prashant Adiga

Abstract
Background: In gestational diabetes both the foetus and placenta experiences a diversity of structural and functional changes. While the changes in the placenta such as placental size, oedema, associated placental abnormalities and microscopic changes such as syncytial knots have been extensively studied, the information on the umbilical cord morphometry is scanty and hence is an area of interest.
Objective: To study the various umbilical cord morphometric indices in pregnancies complicated by abnormalities of glucose metabolism of varying degrees.
Methods: Initial screening for gestational diabetes was done using standard two step protocol (spot test / glucose challenge test - GCT and glucose tolerance test - GTT if spot test result was abnormal). Umbilical Cord Cross Sectional Area (UCCSA), Umbilical Artery Cross Sectional Area (UACSA), Umbilical Vein Cross Sectional Area (UVCSA) and Wharton's Jelly Area (WJA) were measured in pregnant woman after 34 weeks of gestation at the time of third trimester scan. Scans were repeated every two weeks till the woman delivered.
Results: Out of 250 patients recruited for the study, there were 54 patients of abnormal spot test. Among them only 21 had true Gestational Diabetes (GDM) and rest 33 had impaired glucose tolerance (IGT). Umbilical artery and vein area, Wharton's jelly area and total area were significantly higher in GDM group compared to normal controls. Sub-analysis indicated that these values are also higher in IGT group followed by abnormal GCT group compared to normal controls indicating that glucose abnormalities of varying degrees affects these measurements.
Conclusion: There is a positive association between abnormal glucose metabolism and umbilical cord parameters such as artery and vein area, Wharton's Jelly content and total cord area. These changes may occur to ensure enough nutrient supply to the foetus, which has as such increased body composition which is a response to maternal hyperglycemia.

Keywords: Umbilical cord cross sectional area (UCCSA), umbilical artery cross sectional area (UACSA), umbilical vein cross sectional area (UVCSA) and Wharton's jelly area (WJA)

Introduction
The umbilical cord constitutes one of the important organs of the fetus. Foetal health depends much upon normal functions and structure of the umbilical cord. It is the only gateway between the mother and the foetus and hence its dimensions have been linked to nutrient supply to the baby. The umbilical cord morphometry has been studied in a variety of pregnancy complications such as Rh isoimmunised pregnancy [1], small for gestational age [2] and diabetes mellitus [3]. Previously we have studied role of various umbilical cord morphometric indices in pregnancies associated with aberrant foetal growth [4]. Search of literature indicated that foetuses in pregnancies complicated with gestational diabetes had larger umbilical cord [5]. We relooked into our database and segregated those pregnancies who had gestational diabetes and compared the various umbilical cord parameters such as Umbilical Cord Cross Sectional Area (UCCSA), Umbilical Artery Cross Sectional Area (UACSA), Umbilical Vein Cross Sectional Area (UVCSA) and Wharton's Jelly Area (WJA) in different categories of abnormalities of glucose metabolism such as abnormal glucose challenge test (GCT) also known as spot test, impaired glucose tolerance (IGT) and gestational diabetes (GDM).

Materials and methods
This study was a prospective observational study conducted in a tertiary hospital belonging to a medical college having under graduation, post-graduation and super specialization in various courses. 250 pregnant women were enrolled for the study over a period of 2 years.

The procedure for ethical conduct of the study was strictly followed. The study was basically an ultrasound based study where in pregnant women underwent two weekly assessment of umbilical cord parameters in the third trimester and the findings of last ultrasound were considered for calculating the various umbilical cord parameters. The following were the inclusion and exclusion criteria.

Inclusion criteria

1. Single foetus
2. Period of pregnancy >34 weeks
3. Anatomically normal umbilical cord
4. No history of rupture of membranes
5. Women who have undergone Gestational Diabetes screening using the standard protocols.

Exclusion criteria

1. Multifoetal gestation
2. Intrauterine foetal demise
3. Foetuses with known anomalies
4. Leaking membranes
5. Women who did not undergo GDM screening.

Spot test (also known as Oral Glucose Challenge Test - GCT) was performed according to the criteria laid down by O'Sullivan and Mahan [6]. Irrespective of the prandial state, the pregnant woman between 24 to 28 weeks of gestation was administered 50 grams of oral glucose dissolved in plain water and venous blood was drawn on hour later for estimating plasma glucose level. The patient was considered screen positive whenever the value exceeded 140 mg/dL and she was next scheduled for oral Glucose Tolerance Test (GTT).

The patient was instructed to be on minimum of 150 gram of carbohydrate diet per day during 3 days before the scheduled GTT. She was asked to report to the lab in empty stomach after 12 hours of fasting. Fasting venous blood sample was obtained and she was administered 100 grams of oral glucose in 200 mL of water. The blood samples were drawn thereafter every hourly for 3 samples. We used Carpenter and Coustan criteria to identify Gestational Diabetes Mellitus cases [7] with the cut off values of fasting plasma glucose ≥95 mg/dL, at 1 hour ≥180 mg/dL, at 2 hours ≥155 mg/dL, at 3 hours ≥140 mg/dL to diagnose abnormalities of glucose metabolism. Diagnosis of GDM was made whenever the patient had any single value more than 200 mg/dL or any two values above the cut off criteria mentioned.

We considered various dating parameters such as LMP recall, ultrasonically assessed crown rump length measurements before 14 weeks of pregnancy. We used Philips HD11XE ultrasound equipment to obtain umbilical cord study variables in question.

The measurement of the umbilical cord parameters was done in a free loop of umbilical cord according to the method described by Binbir *et al.* [8] The trans-abdominal probe was held perpendicular to the cord length as much as possible. To get clear images, we saw to the point that umbilical cord section was surrounded by good amount of liquor amni. The area of interest was further zoomed (Figure 1) and the circumference of the umbilical cord was traced as accurately as possible using ultrasound machine caliper. Software of the ultrasound machine automatically calculated the cross sectional area in mm^2. Similarly measurements were obtained for both the umbilical arteries and veins and values for both arteries were averaged. Wharton's Jelly area was obtained from deducting area of vein and both arteries from the total area.

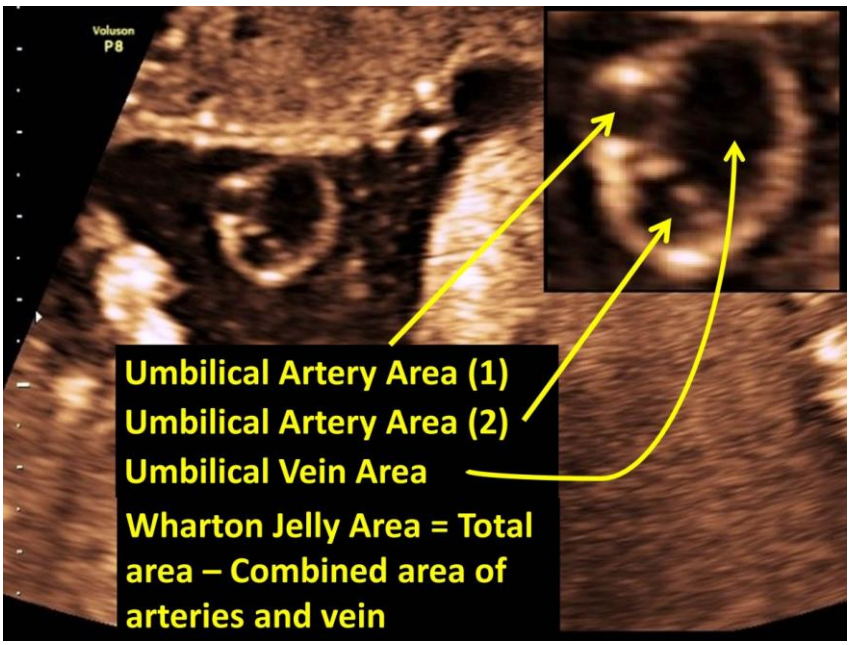

Fig 1: Method of obtaining various umbilical cord parameters by ultrasound

Sample size estimation

Al Maini *et al.* [9] studied umbilical cord dimensions in women with gestational diabetes and reported that cross sectional area of the umbilical cord (mm^2) was 282 ± 50 (mean ± SD). We hypothisised that mean umbilical cord cross sectional area may be 5% (14.1 mm^2) less in controls in order to be statistically significant. Using these parameters the sample size was calculated using the formula;

$$N = (1.96 * \mu / E)^2$$

where in μ (standard deviation) = 50, E (Margin of Error) = 14.1.

Accordingly we got the sample size of 48 patients, but we recruited 250 patients which further increased the power of the study.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences 16.0 (SPSS Inc. Chicago, Illinois, USA). Demographic variables were computed using descriptive analysis methods available in the software. Comparison of means between different groups was done using one way ANOVA. We considered P *value* of < 0.05 was considered statistically significant.

Results

Among the 250 pregnant women recruited for the study, 150 (60%) were primigravida and 100 (40%) were multigravida. 86.8% women were between 20 to 30 years of age, whereas 13.2% women were older. All women were term patients who delivered between 37 to 40 weeks of gestation. The neonatal birth weight ranged between 1740 to 4180 grams with mean and standard deviation of 2943 grams and 413 grams respectively. Table 1 indicates the umbilical cord morphometric indices such as cross sectional area of entire cord, artery, vein and Wharton's Jelly Area.

Table 1: Descriptive Statistics of the patients, neonates and umbilical cord morphometric parameters.

	Mean	SD	Min	Max
Age (Years)	27	3.5	18	38
Gestational Age at Delivery (Weeks)	38.5	0.9	37	40
Neonatal Birth Weight (grams)	2943.3	413.5	1740	4180
Umbilical Cord Section Area (mm^2)	203.6	47.5	107	290
Umbilical Artery Section Area (mm^2)	8.3	2.8	3.1	13.6
Umbilical Vein Section Area (mm^2)	37.3	13.4	11.9	62.4
Wharton's Jelly Area	149.7	28.8	88.8	207.3
SD: Standard Deviation, Min: Minimum Value, Max: Maximum Value				

Figure 2 indicates the consort statement of patients recruited and prevalence of abnormalities of carbohydrate metabolism. There were 54 patients of abnormal spot test with criteria as mentioned in materials and methods. Among them only 21 had true Gestational Diabetes (GDM) and rest 33 had impaired glucose tolerance (IGT). This differentiation was made to study the effect of varying glucose metabolism over the umbilical cord parameters.

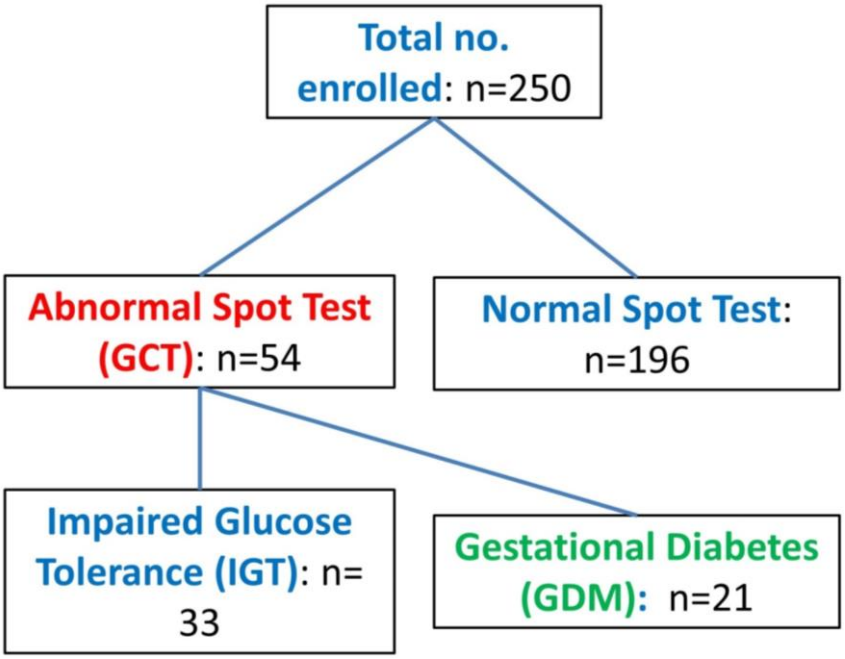

Fig 2: Consort statement

First we compared umbilical cord indices in genuine GDM cases (n=21) and remaining patients (n=229). It can be seen from Table 2 that all the parameters were significantly higher in patients with GDM compared to other group who did not satisfy the laboratory criteria for GDM.

Table 2: Umbilical cord Morphometry in patients with and without Gestational Diabetes (n=250).

	GDM (n=21)	No GDM (n=229)	Anova Statistics	
Parameters (mm^2)	**Mean ± SD**	**Mean ± SD**	**"F" Value**	**P Value**
Artery Area (UACSA)	10.48 ± 3.13	8.1 ± 2.68	109.6	<0.001
Vein Area (UVCSA)	47.66 ± 14.8	36.35 ± 12.83	14.6	<0.001
Wharton's Jelly Area(WJA)	170.11 ± 31.1	147.86 ± 27.86	12.1	<0.001
Umbilical Cross Sectional Area (UCCSA)	239.71 ± 51.44	200.24 ± 45.87	13.9	<0.001

Then we studied whether slight impairment of glucose levels as in cases of impaired glucose tolerance (abnormal values of plasma glucose but not satisfying the criteria for GDM) influences the umbilical cord measurements. Accordingly there were 33 cases of impaired glucose tolerance compared to 196 women with normal GTT findings. Surprisingly we noted that umbilical cord measurements were significantly higher in women with impaired glucose tolerance (Table 3) compared to those with normal GTT values. However these values were still lower compared to frank GDM cases.

Table 3: Umbilical cord Morphometry in patients with and without Impaired Glucose Tolerance (n=229).

	Normal GTT (n=196)	Impaired Glucose Tolerance (n=33)	Anova Statistics	
Parameters (mm^2)	**Mean ± SD**	**Mean ± SD**	**"F" Value**	**P Value**
Artery Area (UACSA)	8.02 ± 2.62	8.55 ± 3.05	7.9	<0.001
Vein Area (UVCSA)	36 ± 12.53	38.48 ± 14.57	7.8	<0.001
Wharton's Jelly Area(WJA)	147.32 ± 27.03	151.11 ± 32.65	6.3	<0.001
Umbilical Cross Sectional Area (UCCSA)	199.02 ± 44.83	207.52 ± 51.79	7.5	<0.001

The sub-analysis was further carried out to find out whether even abnormal spot test values can influence the measurement of umbilical cord. The umbilical cord morphometric indices were compared in abnormal spot test group (n=54) and normal spot test group (n=196). Again it was found that the indices were relatively more in abnormal spot test group compared to normal spot test group, indicating that even subtle changes in the glucose values can influence the umbilical cord parameters.

Table 4: Umbilical cord Morphometry in patients with and without Abnormal Spot Test (GCT) (n=250).

	Normal Spot Test (n=196)	Abnormal Spot Test (n=54)	Anova Statistics	
Parameters (mm^2)	**Mean ± SD**	**Mean ± SD**	**"F" Value**	**P Value**
Artery Area (UACSA)	8.02 ± 2.62	9.3 ± 3.2	9.18	<0.01
Vein Area (UVCSA)	36 ± 12.53	42.05 ± 15.21	8.98	<0.01
Wharton's Jelly Area(WJA)	147.31 ± 27.03	158.5 ± 33.11	6.55	<0.01
Umbilical Cross Sectional Area (UCCSA)	199.02 ± 44.83	220.04 ± 53.56	8.53	<0.01

Thus varying degrees of abnormalities of glucose metabolism such as abnormal spot test values, impaired glucose tolerance and frank gestational diabetes had their influence on umbilical cord parameters in the order of increasing trend. Figure 3 gives overall visualisation of these changes in different groups.

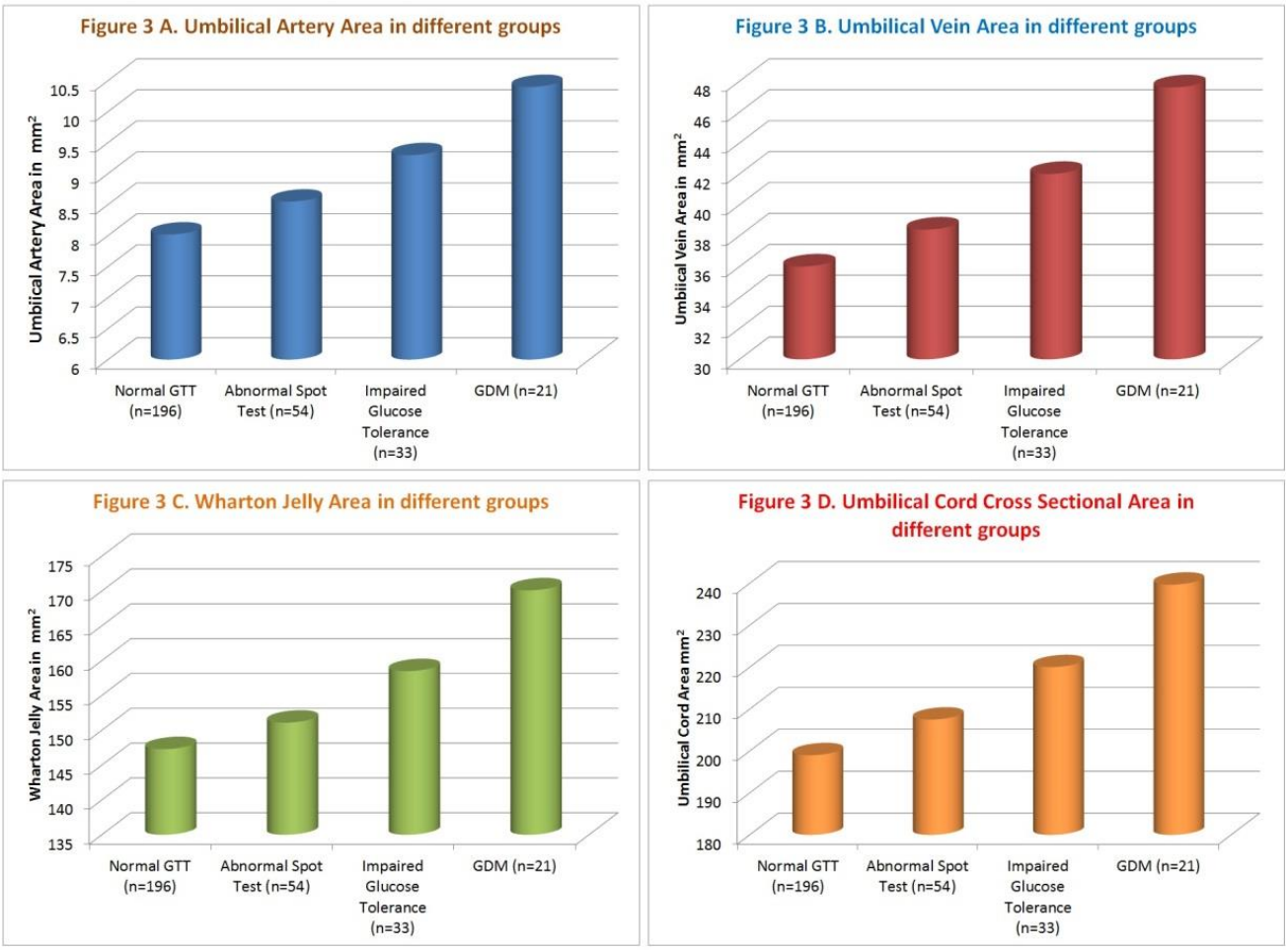

Fig 3: Graphical representation of various umbilical cord morphometric indices in different groups of glucose metabolism

Discussion

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degree with its onset or first recognition during pregnancy. It is well known that various maternal and fetal complications coexist with uncontrolled diabetes which includes polyhydramnios, macrosomia, operative interference, shoulder dystocia, birth injuries and increased perinatal mortality. The basic mechanism includes transfer of elevated maternal glucose via the placenta and the baby responds by hyperinsulinaemia which accelerates foetal growth and fat deposition resulting in increased foetal body composition. The umbilical cord also responds by increasing its diameters of vascular components which includes normally two umbilical arteries and one umbilical vein. However there are only few studies which have extensively addressed the various morphometric indices of umbilical cord in gestational diabetes which include cross sectional area of the umbilical cord, umbilical artery and vein areas and content of the Wharton's jelly which are particularly addressed in the present study.

We analysed neonatal birth weights in normal glucose tolerance (2916gm), impaired glucose tolerance (2941gm) and in gestational diabetes (3201gm) and it was seen that birth weight increased as laboratory values indicated increasing decree of altered glucose metabolism. Whether the increase in body weight is initial event followed by changes in the umbilical cord dimension or vice versa is still not known and may be of interesting proposition to the research scholars.

The earlier studies were mostly based on postnatal examination of the umbilical cord sections. Chakraborty *et al* made dye imprints of cut section of umbilical cord on white paper and measured its contents using AutoCAD computer program [10]. They found that mean ± SD of umbilical cord cross sectional area was 97.97 ± 36.62 mm^2 in diabetic pregnancies and 81.66 ± 24.77 mm^2 in normal controls. Similarly Wharton's Jelly area was found to be 86.60 ± 36.78 mm^2 and 70.96 ± 24.27 mm^2 in these two groups. However these values are much lesser compared to findings of our study because these measurements have been taken after the delivery when umbilical cord normally empties and its vessels along with Wharton's jelly physiologically shrink in response to temperature changes. Ultrasound based studies are done on live foetuses with intact umbilical cord blood flow and cord temperature is maintained at normal body temperature and hence cannot be compared with invitro studies of the umbilical cord.

Weissman and Jakobi found that the umbilical cord was significantly larger in fetuses of mothers with gestational diabetes than in the normal controls and they attributed this phenomenon to an increase in Wharton jelly content [11]. They were of the opinion that estimation of Wharton's jelly may be an important parameter that can differentiate two important foetal growth abnormalities such as small for gestational age (SGA) and large for gestational age (LGA) from appropriately growth fetuses (AGA).

Nidhi Jain and Abha Singh extensively studied Umbilical Cord Cross Sectional Area (UCCSA) in pregnancies complicated by gestational diabetes. They measured UCCSA at 30-32 weeks they found that UCCSA was 239.7 mm^2 in pregnancies complicated by GDM and 224 mm^2 in normal controls. At 36-38 weeks also, UCCSA was significantly larger in GDM (250.1 mm^2) than in controls (228.2 mm^2). They concluded that a strong positive correlation exists between umbilical cord area and birth weight in women with gestational diabetes mellitus, thus it should be estimated during routine antenatal ultrasound for prediction of birth weight in these women [12].

In fact, probably ours is the only study which has looked into the various morphometric indices related to the umbilical cord according to the degrees of impaired glucose metabolism. It is well proven that gestational diabetes is associated with increased umbilical cord dimensions. We have shown that these abnormalities begin with subtle changes in the glucose metabolism, minimal changes in abnormal spot test, moderate changes in impaired glucose tolerance and maximum changes in gestational diabetes.

Conclusion

This study shows that there is a strong positive association between abnormal glucose metabolism and umbilical cord parameters such as artery and vein area, Wharton's Jelly content and total cord area. These parameters show an increasing trend as the glucose metabolism starts becoming abnormal. These changes may occur to ensure enough nutrient supply to the foetus, which has as such increased body composition in response to maternal hyperglycemia. Whether the former or the latter is a primary response to maternal elevated glucose levels is still to be explored. The phenomenon of sudden intrauterine demise in diabetic pregnancies may be partially explained when these adaptive changes do not occur in the umbilical cord, mainly in the content of Wharton's Jelly.

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Conflict of interest: None

Ethical approval: The study was approved by the Institutional Scientific Committee

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