ORIGINAL ARTICLE

Relationship between Ultrasound Measurements of Fetal Adipose Subcutaneous Tissue and Polyhydramnios with Gestational Diabetes Mellitus

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Abstract

Background: Gestational diabetes mellitus (GDM) typically diagnosed by the oral glucose tolerance test (OGTT) between 24 weeks and 28 weeks may miss diagnosis of GDM. Hence, alternative predicators have to be found to classify women as high risk for GDM and keep them under regular follow-up.

Aim and objective: To assess the relationship between ultrasound measurements of fetal adipose subcutaneous tissue (ASCT) and polyhydramnios with GDM in a high-risk population attending a teaching hospital of South India.

Materials and methods: This cross-sectional study with prospective data collection was performed among 120 women with singleton pregnancies after 23 weeks with at least one risk factor for GDM. Fetal ASCT and polyhydramnios on ultrasound were measured and correlated with GDM, which was diagnosed by Diabetes In Pregnancy Study Group India (DIPSI) criteria.

Results: Total 11 (9.2%) of 120 study participants were diagnosed to have GDM. About 65.91% of GDM women had increased ASCT ($p < 0.0001$) and 56.82% had polyhydramnios ($p < 0.0001$). The ASCT was significantly higher in GDM ($p < 0.0001$). Univariate logistic regression showed thickened ASCT and polyhydramnios to be highly significant predictor of GDM ($p < 0.0001$).

Conclusion: There is a strong correlation between thickened ASCT and polyhydramnios with GDM and can be incorporated into regular ultrasound scan after 24 weeks, thereby ensuring that no pregnant woman with GDM is missed. Further studies are recommended to explore other USG parameters with GDM.

Keywords: Fetal adipose subcutaneous tissue, Gestational diabetes mellitus, Polyhydramnios, Ultrasonography.

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Introduction

Diabetes is a major public health problem in India with prevalence rates reported to be between 4.6 and 14% in urban areas and 1.7 and 13.2% in rural areas. Not surprisingly, in parallel with the increase in diabetes prevalence, there seems to be an increasing prevalence of gestational diabetes mellitus (GDM), that is, diabetes diagnosed during pregnancy. The prevalence of GDM has been reported to range from 3.8% in Kashmir[1] to 6.2% in Mysuru,[2] 9.5% in Western India,[3] and 17.9% in Tamil Nadu.[4] In more recent studies, using different criteria, prevalence rates as high as 35% from Punjab[5] and 41% from Lucknow have been reported.[6] The geographical differences in prevalence have been attributed to differences in age and/or socioeconomic status of pregnant women in these regions. It is estimated that about 4 million women are affected by GDM in India, at any given time point.[7]

There is no international consensus regarding timing of the screening method and the optimal cutoff points for diagnosis and intervention of GDM. Diabetes In Pregnancy Study Group India (DIPSI) recommends nonfasting oral glucose tolerance test (OGTT) with 75 g of glucose with a cutoff of ≥140 mg/dL after 2 hours, whereas the WHO (1999) recommends a fasting OGTT after 75 g glucose with a cutoff plasma glucose of ≥140 mg/dL after 2 hours. The recommendations by ADA/IADPSG for screening women at risk of diabetes are as follows: for first and subsequent trimester at 24–28 weeks, criteria of diagnosis of GDM are made by 75 g OGTT and fasting 5.1 mmol/L, 1 hour 10.0 mmol/L, 2 hour 8.5mmol/L by universal glucose tolerance testing. Critics of these criteria state that it causes overdiagnosis of GDM and unnecessary interventions; the controversy however continues. The American College of Obstetricians and Gynecologists (ACOG) still prefer a two-step procedure, GCT with 50 g glucose nonfasting if value >7.8 mmol/L followed by 3-hour OGTT for confirmation of diagnosis.[8]

Obstetrical ultrasound is used for visualization of the placenta, amniotic fluid, embryo, and fetus *in utero*. It is a standard part of prenatal diagnostic procedures and provides a wide range of information regarding the health of the mother and the fetus and the way of progress of pregnancy. Ultrasound screening for fetal biometry and abnormality is widely practiced and there are defined sonographic markers of GDM.[9]

More effective and simpler strategies need to be developed in future clinical practice by which the need for performing an OGTT can be avoided.[8] Thus, it is preferable to explore alternative markers

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and scales or tests to classify women as high risk for GDM and keep them under regular follow-up.

Hence, this study was planned to assess the relationship between ultrasound measurements of fetal adipose subcutaneous tissue (ASCT) and polyhydramnios with GDM and check if it can be used as a predictor for GDM.

Materials and Methods

This prospective cross-sectional study was conducted between January 1, 2016 and June 31, 2017, in JSS Hospital, Mysuru. All women attending the Outpatient Department of Obstetrics and Gynaecology in JSS Hospital, Mysuru, satisfying the inclusion and exclusion criteria and providing a written informed consent were be considered for the study.

Women with singleton pregnancies after 24 weeks of gestation were included in the study, who had pregnancy-related risk factors for GDM such as polyhydramnios and/or macrosomic fetal growth in the current pregnancy or had at least one maternal risk factor for GDM, viz., BMI >30, multiparity, advanced maternal age >35 years, previous delivery of a macrosomic baby more than 4,000 g at birth, polycystic ovary syndrome, family history of diabetes, and previous neonatal and perinatal loss.

Women with any preexisting diseases or having confirmed fetal abnormalities or diagnosed as GDM in present pregnancy before 24 weeks were excluded from the study.

After obtaining an informed consent, medical and obstetric history of the study participants was recorded by personal interview with a pretested, structured questionnaire. The study participants were then subjected to an obstetric ultrasound scan to measure the ASCT and check for polyhydramnios.

Ultrasound examination was performed using a Logic 3 expert scanner with a variable 2–5 MHz transducer (General Electric Medical Systems, Milwaukee, Wisconsin, USA). Increased ASCT was defined as >4.4 mm (23–25), >5.5 mm (26–28), >6.6 mm (29–31), >7.7 mm (32–34), >8.8 mm (35–37), and >9.1 mm (38–40).[10] Polyhydramnios was defined as >220 mm (24–26), >225 mm (27–29), >235 mm (30–32), >245 mm, (33–37), and >240 mm (38–39).[11]

The scan was followed by glucose level estimation the next day. Venous blood was collected from every participant for blood glucose estimation after 2 hours of the participant consuming 75 g of glucose (OGTT). Blood glucose was measured using the glucose oxidase peroxidase (GOP) method in values of mg/dL. Gestational diabetes mellitus was diagnosed based on the recent DIPSI criteria.[12] The OGTT was done as the last test to avoid any sort of bias by the interviewer.

Data were entered in the Microsoft Excel software and analyzed using the Epi-Info software package. Descriptive and inferential statistics were used to analyze data. Descriptive statistics, viz., measures of central tendency and measures of variability (arithmetic mean with standard deviation, median with interquartile range, minimum and maximum values, as well as the relative numbers for categorical variables). The following methods of inferential statistics were used to assess the significance of difference: the Student's *t*-test for independent samples and the rank-sum test for numerical variables, depending on the normality of distribution, and the chi-square test and the Fisher's exact test, depending on the numerical limitations.

Results

The study included 120 pregnant women who had fulfilled the inclusion criteria and provided an informed consent. None of the women were of gestational age less than 24 weeks, and they had at least one of these risk factors for diabetes in pregnancy. The data were collected by the interview method and the patients underwent ultrasonographic scan in our hospital followed by a 2-hour 75 g glucose OGTT.

Total 11 (9.2%) of 120 study participants were diagnosed to have GDM by the DIPSI criteria.

Thickened ASCT measured ultrasonographically was very highly significantly increased among participants with GDM ($p < 0.0001$) and also there was significantly higher occurrence of polyhydramnios in GDM women when compared to normal women ($p < 0.0001$) as seen in Tables 1 and 2.

Thickened ASCT (65.9%) and polyhydramnios (56.8%) had good sensitivity, i.e., have the ability to identify the highest number of true positives and 94.3 and 84.1% specificity, respectively, i.e., the ability to correctly identify true negatives for GDM (Table 3).

Thickened ASCT (84.7%) and polyhydramnios (79.6%) have the high negative predictive value (the probability of not having a disease in a subject with a negative test result) and good positive

Table 1: Results of thickened adipose subcutaneous tissue (ASCT) and polyhydramnios ultrasonographic measurements in participants

	OGTT				
	Normal		*Pathological*		
Variable	*n = 109*	*%*	*n = 11*	*%*	*p*
Thickened ASCT	6	5.68	7	65.91	<0.0001
Polyhydramnios	17	15.91	6	56.82	<0.0001

OGTT, oral glucose tolerance test

Table 2: Results of thickened adipose subcutaneous tissue (ASCT) and polyhydramnios ultrasonographic measurements on participants

OGTT result		*n*	*X*	*SD*	*t*	*p*
ASCT*	Normal	109	5.855	1.4931	−7.336	<0.0001
	Pathological	11	8.043	1.8392		
AFI**	Normal	109	144.95	38.923	−5.61	<0.0001
	Pathological	11	187.93	46.259		

* values in mm; **values expressed in the degree of maturity at Grannum classification

n, number of patients; *X*, mean value; SD, standard deviation; *t*, the value of test, OGTT, oral glucose tolerance test; AFI, amniotic fluid index

Table 3: The specificity, sensitivity for detection of gestational diabetes mellitus by thickened adipose subcutaneous tissue (ASCT) and polyhydramnios ultrasonographic measurements in study population

	Specificity		*Sensitivity*	
	(%)	*95% CI*	*(%)*	*95% CI*
Thickened ASCT	*94.3*	*89–99*	*65.9*	*52–80*
Polyhydramnios	84.1	91–100	56.8	42–71

Table 4: The negative and positive predictive value of the ultrasonographic markers in study population

	NPV (%)*	*95% CI*	*PPV** (%)*	*95% CI*
Thickened ASCT	*84.7*	*77–91*	*85.3*	*68–94*
Polyhydramnios	79.6	70–87	64.1	47–78

*NPV, negative predictive value; **PPV, positive predictive value
ASCT, adipose subcutaneous tissue

Table 5: Relationship between USG markers and gestational diabetes mellitus by logistic regression

	Univariate analysis		
Parameter	*p*	*RR*	*95% CI*
Thickened ASCT	<0.0001	32.09	10.72–96.11
Polyhydramnios	<0.0001	6.96	3.05–15.86

ASCT, adipose subcutaneous tissue

predictive value (the probability of having the state/disease of interest in a subject with positive result), viz., 85.3 and 64.1%, respectively (Table 4).

The univariate regression model showed that both the USG parameters had a very highly significant relationship with GDM with thickened ASCT (RR: 32.09, 10.72–96.11, $p < 0.0001$) having the highest RR (Table 5).

Discussion

This study was conducted from January 1, 2016 to June 31, 2017 (18 months) in JSS Hospital, Mysuru. All women attending the Outpatient Department of Obstetrics and Gynaecology in JSS Hospital, Mysuru, satisfying the inclusion and exclusion criteria and providing a written informed consent were considered for the study. The study included 120 pregnant women. None of the women were of gestational age less than 24 weeks, and they had at least one of these risk factors for diabetes in pregnancy. Total 11 (9.2%) of 120 study participants were diagnosed to have GDM by the DIPSI criteria.

Increased Adipose Subcutaneous Tissue

As early as in 1977, the work of "Subcutaneous Fat in Newborn Infants of Diabetic Mothers: An Indication of Quality of Diabetic Control" was published in the Lancet in which Whitelaw proved that ASCT is a stronger index of maternal glycemia control compared to the glycemic profiles that are done during pregnancy.[13] This observation, together with the results of other studies, suggest that increased thickening of fetal subcutaneous tissue can be used not only in the prediction of GDMs but also as a new criterion of direct assessment of fetal metabolic status instead of traditional methods of indirect evaluation based on the values of maternal glycemia. Disproportionate growth of the fetus is often evident only in the third trimester. However, ASCT increase in inadequate maternal metabolic control can be detected early in pregnancy as shown by Perovic et al.[9] and Gojnic et al.[14] This can be used not only for early diagnosis of GDM but also for determining the moment of introduction of insulin therapy and its proper dosage in patients where dietary regime and moderate physical activity did not achieve the desired therapeutic results. This is of great importance if one bears in mind the importance of good metabolic control in pregnant women from the second trimester of gestation, because the slightest degree of maternal hyperglycemia may be responsible for complications in pregnancy and its outcome.

The importance of ASCTs is emphasized by the findings of Greco and associates.[15] The authors concluded that the deposition of body fat increased in all patients with diabetes, even in well-controlled patients (Greco et al., 2003).[15] From this, we can draw two conclusions. First, the ASCT as ultrasound markers of GDM is superior in prediction of this entity, or impaired glycemic control, in relation to conventional methods of determining the different types of blood glucose (fasting, postprandial, random). This was also confirmed by the study done by Gojnić and associates published in 2012.[14] The second conclusion is that the increased fetal adipose tissue measurements explain the occurrence of fetal macrosomia in pregnancies that are believed to be well controlled, but in fact, they were pregnancies that through conventional methods we failed to detect the disturbance of glycemic control.

Polyhydramnios

Although the use of amniotic fluid index (AFI) values in the assessment of fetal condition entered in application decades earlier, its popularity continues to grow despite the development of far more sophisticated ultrasonographic methods, such as Doppler evaluation of the uteroplacental, fetoplacental, and fetal circulation. Interconnection of abnormal AFI value with adverse perinatal outcome has long been documented. However, new studies have entered into more subtle assessment of this issue. Some have analyzed AFI value changes that occur in pregnancies complicated with diabetes. Kofinas and Kofinas showed that adverse pregnancy outcome with abnormal AFI values is even more frequent in case of pregnancies complicated by diabetes.[16]

The AFI values of patients whose pregnancies are complicated by diabetes showed significantly different schemes of common values during different periods of pregnancy when compared to healthy pregnant women. Moore presented possible theories to explain this phenomenon, and the interaction of the maternal glycemic status and the AFI value.[11] The first says that maternal hyperglycemia induces fetal hyperglycemia, which when crossed a certain threshold results in osmotic diuresis in fetus, and hence greater production of amniotic fluid. Another speaks of glucose as equalizer at the placental level, which leads to isotonic movement of water into fetal compartments. This leads to expansion of the volume of bodily fluids in fetus and consequent increase in the glomerular filtration rate and increased production fetal urine. A third theory states that increasing the amount of amniotic fluid occurs as a result of decreased fetal swallowing of amniotic fluid, which is not followed by concomitant change in fetal urine.

Increased AFI value in patients with unsatisfactory glycemic control was revealed in a study done by Gojnic et al. in 2012. This study showed that in the third trimester of pregnancy, there is a high degree of correlation between the value of the AFI in patients with good and patients with unsatisfactory glycemia ($F = 79.234$,

$p < 0.001$, ETA2U = 0.222). Control of blood glucose in 2 hours postprandial values only sporadically pointed to inadequate glycemic regulation, unlike ASCT and AFI values, which are observed more clearly and consistently.

Drawbacks of Oral Glucose Tolerance Test and Need for Ultrasound markers

Criticism of OGTTs in screening and diagnosis of GDM (GCT and OGTT) relates to the practical problem of sensitivity and reproducibility, which are related to the time interval between the tests and between them and the carbohydrate intake.

Subsequently, exposure to carbohydrates increases insulin sensitivity and glucose utilization. That in physiology is known as the Staub-Traugott phenomenon, which reduces the sensitivity of tests with oral glucose load.[17] Reliability and repeatability of these tests is also very poor. Study by Harlass et al. and Brody et al. have shown that as much as 23% of pregnant women with a positive value of GCTs have contradictory answers to two successive OGTTs, which were performed after 1 week.[18]

Another problem is that in countries with developed healthcare system and firmly established screening programs, up to 30% of high-risk patients are not tested for a period of 24–28 weeks with GCT due to organizational reasons and oversight.[19] The logical solution that arises in relation to these two problems is that GCT is performed after 28 weeks of gestation. However, physiological changes during pregnancy and results of studies that deal with the issue of performance GCT during pregnancy call into question the validity of the use of conventional methods screening after the 28th week of pregnancy. In contrast, ultrasound examinations are routinely performed after the 28th week of pregnancy. In addition, the proposed ultrasound markers for the detection of GDM do not depend on the level of anti-insulin hormone, which promotes these markers as a reliable alternative method of screening at this time. In addition, from a practical point of everyday preventive and clinical labor, this increases the detection rate of the disease.

Clinical Significance

The clinical significance of ultrasound findings of ASCT and polyhydramnios is that it could provide early diagnosis and earlier initiation of the therapy regimen, which will result in a reduction of the negative effects that this pathological entity carries. Further studies can be planned on a larger scale in different centers to validate the same.

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