The Role of Mid-Trimester Ultrasound Fetal Liver Length Measurement in Prediction of Gestational Diabetes Mellitus

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Abstract: Introduction: Gestational diabetes mellitus (GDM) is a preventable leading cause to adverse maternal and neonatal outcomes but globally agreed diagnostic criteria remain inconclusive, so Identification of women with GDM is important, as treatment reduces the adverse outcomes. **Aim of the work**: Assess the relation between mid - trimester ultrasound measurement of fetal liver length (FLL) in the screening of GDM in high-risk population of pregnant women. **Patient and methods:** A total of 150 with singleton pregnancies with high risk factor (s) to develop GDM underwent sonographic examination at 20–24 weeks with FLL measurement and correlate this finding by results of 2 hours 75 gm oral glucose tolerance test (OGTT) which was done at 24-28 weeks gestation. **Results:** The prevalence of GDM was 16% in the studied population, the maternal age, body mass index (BMI) and past history of GDM were significant risk factors. The mean FLL in GDM was significantly higher than in healthy women (36.55 vs 33.93 mm, respectively; P<0.001). Liver enlargement was related to maternal fasting glucose levels not 1st or 2nd hour glucose level. **Conclusion:** The present study demonstrate increased ultrasound FLL measurement and development of GDM. Key words: gestational diabetes mellitus, fetal liver, OGTT, risk factors. **List of abbreviation:** Gestational diabetes mellitus (GDM), fetal liver length (FLL). oral glucose tolerance test (OGTT), body mass index (BMI) IUFD (intra-uterine fetal death).
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1. Introduction

GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy. [(1)] In normal pregnancy, there is a progressive physiologic increase of insulin resistance compensated by an increase of insulin secretion by pancreatic β - cells. Among GDM women there is an imbalance between insulin resistance and insulin secretion capacity resulting in increased circulating glucose levels [(2)].

Randomized controlled trials have confirmed that in routine antenatal care identification and treatment of GDM even in its mildest form reduces the incidence of hypertensive disorders, Caesarean section, macrosomia and shoulder dystocia [(3)]. The approach to screening and diagnosis of (GDM) around the world is disorderly the protocols for diagnosis vary not only in-between countries, but also within countries. Furthermore, in any country, this disparity occurs in-between its hospitals and often exists within a single hospital. There is lack of an international consensus among preeminent health organizations often there is a disagreement between the country's national diabetes organization [(4)], its local health society and its regional obstetric organization with each one recommending a different option for approaching GDM [(5)] so, identification of women with GDM is important, as treatment reduces the adverse outcomes.

Some of the proposed unconventional screening methods are based on ultrasound examinations, taking into account that these examinations are routinely performed in most women during the course of the pregnancy [(6,7)].

Ultrasonography is a useful, readily available, noninvasive method for the diagnosis and surveillance of fetal conditions as part of the management of diabetic pregnancy. Furthermore, ultrasonography can be used to detect GDM, as well is a helpful guide for the initiation of early therapeutic management for pregnancies complicated by carbohydrate intolerance [(8)]. A mid-trimester ultrasound scan is routinely performed between 18 and 23 weeks gestation, this period of pregnancy is the most suitable for both adequate dating of the pregnancy and the timely diagnosis of congenital anomalies [(9,10)].

Fetal growth is evaluated throughout gestation by measuring various fetal body dimensions, one of these fetal body dimension is fetal liver length (FLL). Increased glucose transfer from the diabetic mother to the fetus and placenta results in fetal hyperglycemia and hyperinsulinemia, promoting growth of insulin-dependent tissues and organs, such as the liver [(11)].

Aim of the Work

The aim of the study is to test correlations between blood glucose levels by an (OGTT) with (FLL) evaluated during mid-trimester ultrasound examination and to assess the value of these measurements in the screening of GDM in high-risk pregnant women.

2. Patients and Methods

This is a prospective study which was carried out at Alzahraa University hospital, Cairo, Egypt, department of obstetrics and gynecology and the outpatient clinic. 150 women with singleton pregnancy were recruited from the outpatient clinic. **Inclusion criteria**: A singleton pregnancy at gestational age between 20 -24 weeks determined on the basis of the last normal menstrual period or by early ultrasound measurement of fetal crown–rump length, Presence of one or more risk factor for GDM which include BMI>30 kg/m2, multiparity, maternal age >35 years, previous delivery of a macrosomic baby [>4000 g], history of previous GDM, history of polycystic ovary syndrome, family history of diabetes, history of unexplained IUFD and history of delivery of baby with congenital anomalies). **Exclusion criteria**: Women with a multiple pregnancy, history of hypertension, type 1 or 2 diabetes, pregnant women on long-term medical treatment that may have affected glucose metabolism (corticosteroids, B blocker, antipsychotics). **At the first visit (20-24 weeks):** A verbal consent to all participants enrolled in the study was taken from the patient after explanation of the nature and purpose of the study. Full history was taken and baseline data were collected during the first antenatal visit including personal history (age, parity, gravidity, smoking, residence) height, Past medical history, family history and obstetric history. Complete general and abdominal examination with stress on BMI (weight in kg/height in meter^2).

Ultrasound examination using 3.5-MHz transducer of the Medeson SONOACE R3 ultrasound machine (Samsung electronics, Korea) at 20 -24 weeks (confirming the gestational age, screening for congenital anomalies, assessment of fetal biometry, AFI and the placental site). Measurements of the fetal liver was performed. A sagittal or coronal section of the fetal abdomen was used to measure liver length. The tip of the right lobe of the liver was clearly identified and liver length was measured from the dome of the right hemi-diaphragm to the tip of the right lobe.

At the second visit (24-28 weeks): 75 grams 2 hours OGTT done in the morning after an overnight fast of between 8 and 14 hours. During the three previous days the subject must have an unrestricted diet and unlimited physical activity. The test involves withdrawal of blood sample to measure the fasting plasma glucose level then drinking a carbohydrate load containing 75 gm anhydrous glucose in 250-300 ml of water and withdrawing blood sample to measure glucose levels at 1 hours and 2 hours interval. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

Fasting plasma glucose of 92mg/dl (5.1mmol/l)
1-hour plasma glucose of 180mg/dl (10.0mmol/l)
2-hour plasma glucose of 153mg/dl (8.5mmol/l). (1)

Statistical Analysis: Data were collected, revised, coded and entered to the statistical package for social science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric while qualitative data were presented as number and percentages. The comparison between two independent groups with qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** only when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test. Pearson correlation coefficients*** were used to assess the correlation between two quantitative parameters in the same group. ***Receiver operating characteristic curve*** was used to assess the best cut off point between normal FBS and high FBS with its sensitivity, specificity, positive predictive value, negative predictive value and area under curve. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

3. Results:

The study included 150 pregnant women between 20th and 24th week of gestation (mean gestational age 22.03 ± 1.44 SD) were recruited from the out-patient obstetrics clinics. All patients had singleton pregnancy with risk factor (s) to develop gestational diabetes. According to the results of the 2h 75 gm OGTT the patients were divided into two groups group (I): women show a normal results of the 2h 75 gm OGTT group (II): women show abnormal results for the 2h 75 gm OGTT. The advanced maternal age (mean in group I 30.92 vs 28.54 years in group II P= 0.026) had a significant association with GDM (Table 1). The prevalence of GDM in this high risk population was 16% (24 patients). Analysis of risk factors for GDM (Table 2) in the studied population showed significant association between group II and BMI>30 kg/m2 (54.20% in group II vs 43.3% in group I), also there was high statistical significance in patients with past history of GDM ($p < 0.001$) with no significance regarding previous delivery of macrosomic baby, previous unexplained IUFD, PCO, history of delivery

of baby with congenital anomalies or family history of diabetes.

There was high statistical significance between the fetal liver length measurement by ultrasound at 20-24 weeks and development of GDM (table 3). The average FLL measurement in group II was 36.55± 2.08SD, while it was 33.93 ± 2.43 in group I (P< 0.001).

The ROC analysis (Figure 1) established a cut-off value for FLL of >37.2 mm for the prediction GDM, which has a sensitivity of 50%, specificity 96.83%, positive predictive value 75%, and negative predictive value 91%. When tested as a potential prognostic factor for excluding GDM (Table 4). FLL had a positively correlated to FBS, 1hour and 2hour plasma sugar in all patients and with the FBS in Group II Patients.

Table (1): Comparison between group I and group II as regard the demographic data.

		Group I	Group II	Test value	P-value	Sig.
		No. = 126	**No. = 24**			
Age (years)	Mean±SD	28.54 ± 4.78	30.92 ± 4.51	2.254•	0.026	S
	Range	19 – 39	23 – 37			
	> 35 yrs	16 (12.7%)	6 (25.0%)			
Gestational age (week)	Mean±SD	21.99 ± 1.47	22.25 ± 1.33	0.801*	0.424	NS
	Range	20 – 24	20 – 24			
BMI (kg/m2)	Mean±SD	27.92 ± 5.12	29.65 ± 4.10	1.560•	0.121	NS
	Range	19.2 – 40	21.8 – 36			
Parity	Nullipara	25	5	0.982	0.612	NS
	Secundiparity	55	8			
	3 or more	46	11			

Table (2): Comparison between group I and group II in relation to the risk factors.

		Group I		**Group II**		**Test value**	**P-value**	**Sig.**
		No.126	**%**	**No.24**	**%**			
BMI	<30 kg/m2	84	66.6%	11	**45.83%**	9.681*	0.021	**S**
	>30 kg/m2	42	33.3%	13	**54.20%**			
Delivery of macrosomic baby	Negative	115	91.3%	20	83.3%	1.411	0.235	NS
	Positive	11	8.7%	4	16.7%			
Unexplained IUFD	Negative	116	92.1%	22	91.7%	0.004	0.948	NS
	Positive	10	7.9%	2	8.3%			
History of PCO	Negative	118	93.7%	23	95.8%	0.170	0.680	NS
	Positive	8	6.3%	1	4.2%			
Previous history of GDM	Negative	124	98.4%	19	79.2%	16.785	0.000	HS
	Positive	2	1.6%	5	20.8%			
Previous fetal anomalies	Negative	121	96.0%	23	95.8%	0.002	0.964	NS
	Positive	5	4.0%	1	4.2%			
Family history of DM	Negative	54	42.9%	15	62.5%	3.131	0.077	NS
	Positive	72	57.1%	9	37.5%			

Table (3): The relation between fetal liver length measurement and development of GDM.

		Group I	**Group II**	**Test value**	**P-value**	**Sig.**
		No. = 126	**No. = 24**			
FLL	Mean±SD	33.93 ± 2.43	36.55 ± 2.08	-4.933	0.000	HS
	Range	25.9 – 38	33.5 ± 39.6			

Table (4): Cut of point, sensitivity, specificity, PPV and NPV of FLL in screening of GDM

Cut of point	Sensitivity	Specificity	PPV	NPV
>37.2	50%	96.83%	75%	91%

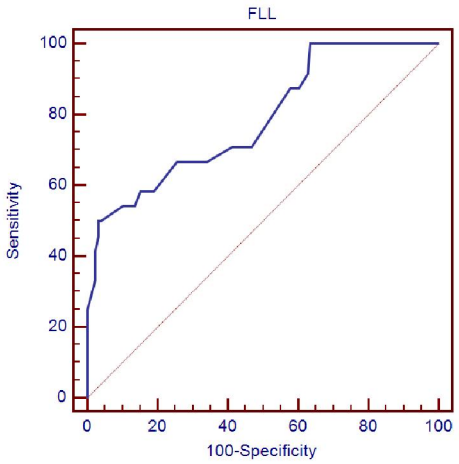

Figure (1): (ROC) curve statistics using different cut-off levels of fetal liver length

4. Discussion

The present study has demonstrated that, there was a highly significant correlation between FLL (measured at 20-24 wks gestation) and development of GDM. The average FLL in normal women was 33.93 ± 2.43 mm in comparison to 36.55 ± 2.08 mm in patient who developed GDM (Pvalue 0.000). The ROC analysis established a cut-off value of FLL of >37.2 mm for the prediction

GDM, with sensitivity of 50% specificity 96.83%, positive predictive value 75%, and negative predictive value 91.9%. Also the FLL measurement was positively correlated to the FBS (P value 0.000) and not to the 1hours (P value 0.873) or 2 hours (P value 0.889) blood suger in patient with GDM.

This results was in agreement with Perovic et al. [8] how reported that the mean FLL were significantly higher in GDM than in healthy subjects (41.04 vs 31.09 mm, respectively; P<0.001). The ROC analysis established a cut-off value of FLL of 39 mm for the prediction GDM, with sensitivity of 71.76%, specificity 97.56%, positive predictive value 91.0%, and negative predictive value 90.9%.

In GDM patients, there was a significant positive correlation (P<0.001) between FLL and blood glucose levels during the OGTT (immediately before and 60, 120, and 180 min) after glucose intake. The slightly higher values regarding FLL may be explained by the difference in GA (our study applied between 20- 24 wks while Perovic et al at 23 wks gestation).

Also our study was in agreement with Mirghani et al. [12] in which total of 123 consecutive healthy pregnant women underwent sonographic examination at 21–24 weeks' gestational age. (15.4%) women were diagnosed with GDM. Measurements for fetal anterior abdominal wall subcutaneous fat, IVS thickness, liver length, and Wharton's jelly area, were measured FLL was the only measurement to show a significant increase among women with GDM (FLL was 36 (32–37)mm in GDM vs 31 (30–33)mm in normal). The maternal fasting glucose level had a significant effect on fetal liver length however, 2-hour postprandial OGTT glucose level did not have a significant effect. A study done by Dimaano and Rivera [13] to determine the fetal liver length measured at 14 to 40 weeks gestational age in diabetic Filipino mothers compared to non-diabetic Filipino mothers, analysis showed that liver lengths for diabetic subjects were larger compared to non-diabetic subjects, but was only significantly in the overt diabetic group.

A study by Roberts et al. [14], on 26 women had type 1 diabetes, 54women had type 2 diabetes. Ultrasonographic measurements were made at 18, 28, and 36 weeks' gestation and reported that the biparietal diameter, femur length, abdominal circumference, and liver length compared with reference values were all significantly increased throughout pregnancy in the diabetic subjects ($p < 0.001$ for all time points) However, the increase in liver length was significantly greater than that of femur length or abdominal circumference at each time point. The mean excess size of femur length and abdominal circumference at 18 weeks had not become significantly more marked by 36 weeks, but for the liver there was a progressive rise from 12.0% at 18 weeks to 16.7% at 24 weeks and 19.3% at 36 weeks, a significant rise between the eighteenth and thirty-sixth weeks ($p < 0.02$). A study [15] in which assessment of fetal liver volume by 3D U/S in pregnancies complicated by insulin-dependent diabetes showed that there was statistically significant difference between fetuses of diabetic women and normal controls for liver volume (45.9 ±34.0 SD vs 38.3±28.7 SD mL P value 0.001), the study demonstrate that the mean liver volume in the diabetes group was 20% higher compared with the normal control group.

Fetal structures grow at a different rate base on their responsiveness to insulin. For instance, muscle and liver tissue are highly sensitive to fetal insulin hence incase in the liver size was noticed in diabetic pregnancies. Naeye [16] found in post mortem specimen liver size in fetuses of diabetic mothers to be increased by approximately 80% when compared with normal controls. This difference was due to both cellular hyperplasia and hypertrophy. Moreover, the enlarged fetal liver in the diabetic group contained more than three times as much haematopoietic tissue as the fetal liver in controls. This abnormal growth is mostly attributable to fetal hyperinsulinaemia [17].

In contrast a longitudinal study [18] including 17 pregnant women with a diagnosis of GDM and a control group of 10 women with normal glucose tolerance women recruited at (24 to 28 weeks of

gestation) with follow-up visits at 32 weeks, 36 weeks, and delivery, Fetal liver volume was evaluated using 3-D ultrasound at each antenatal visit, and fetal liver growth was compared between women with and without GDM. It was found that the fetal liver growth was similar in offspring of women with and without GDM fetal liver volume could be a strong predictor of infant birth weight independent of GDM status. Dubé explaint the discrepancies between his findings and others was related to the small number populations studied and concluded that a larger study has to be carried to further explore the usefulness of measuring fetal liver volume in the estimation of fetal weight and the management of women with GDM.

Also a study done in Alexandria to study the diagnostic ability of the fetal ultrasonographic parameters in screening for gestational diabetes and failed to find a positive correlation between fetal liver length and GDM although maternal hyperglycemia is related to fetal hyperglycemia and hyperinsulinemia, which has a significant impact on the growth of insulin-dependent tissues and organs, such as the liver (FLL mean 31.78± 1.655SD in non diabetic vs 33.71 ± 2.752 SD in patients with GDM P=0.060 NS) **[19].**

5. Conclusion

Science the strategy of screening with the GTT at 24–28 weeks gestation may not always be a feasible option in all circumstances, the suggestion that fetal liver measurements during a mid-trimester ultrasound examination may be predictive of GDM is attractive, but this finding does require further evaluation. Fetal liver measurement remains a possible additional method for the detection of GDM because the procedure does not require a lot of time and effort to obtain the measurements.

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