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ORIGINAL ARTICLE

Relationship between mid-trimester ultrasound fetal liver length measurements and gestational diabetes mellitus

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Abstract

Background: The aim of the present study was to investigate the relationship between mid-trimester ultrasound fetal liver length (FLL) and gestational diabetes mellitus (GDM) in a high-risk population.

Methods: A prospective study was performed in 331 women with singleton pregnancies who were at high risk of GDM and were undergoing a mid-trimester ultrasound examination. The ultrasound scan at 23 weeks gestation was followed by a 100-g oral glucose tolerance test (OGTT) at 24 weeks gestation. Correlations between FLL and OGTT results at different time points were tested. Receiver operating characteristic (ROC) analysis of FLL as a potential prognostic factor for GDM was also performed.

Results: In GDM patients, there was a significant positive correlation ($P < 0.01$) between FLL and OGTT glycemia immediately before and 60, 120, and 180 min after glucose intake. Mean FLL in GDM was significantly higher than in healthy subjects (41.04 vs 31.09 mm, respectively; $P < 0.001$). When tested as a potential prognostic factor for GDM, fetal liver measurements showed excellent diagnostic performance. 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%. The usefulness of FLL measurements was supported by a high area under the ROC curve (90.5%).

Conclusion: In conclusion, there is a strong correlation between FLL and OGTT results, with FLL possibly serving as a valid marker for the prediction of GDM in high-risk populations.

Keywords: correlation, predictive value, sensitivity, specificity, ultrasonography.

Significant findings of the study: In patients with gestational diabetes, there was a significant positive correlation between fetal liver length (FLL) and blood glucose values during the oral glucose tolerance test (OGTT). The usefulness of fetal liver length measurements was supported by high area under the receiver operating characteristic curve.

What this study adds: FLL is strongly correlated with OGTT results and could serve as a valid marker for the prediction of gestational diabetes in high-risk populations.

Introduction

It is important to detect gestational diabetes mellitus (GDM) because of its association with a high risk of perinatal morbidity[1] and increased risk of future diabetes in the mother.[2] To diagnose GDM, as an asymptomatic entity, it must be screened for. The 50-g non-fasting 1-h glucose challenge test (GCT) is the most widely implemented screen used currently, despite its limitations, which include the fact that it is time consuming, costly, may be unpleasant, imposes a supraphysiological glucose load that is unrelated to body weight, and lacks reproducibility (in up to 24% of women). Furthermore, lowering cut-off values in the 1-h GCT to enhance sensitivity invariably jeopardizes specificity.[3] Therefore, alternative screening methods have been proposed to increase the detection rates of GDM and to overcome these shortcomings of the GCT. 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.[4,5]

Ultrasonography is a useful, readily available, non-invasive method for the diagnosis and surveillance of fetal conditions as part of the management of diabetic pregnancy.[6] Furthermore, ultrasonography can be used to detect GDM,[4] as well is a helpful guide for the initiation of early therapeutic management for pregnancies complicated by carbohydrate intolerance.[7,8] Fetal growth is evaluated throughout gestation by measuring various fetal body dimensions. Some of these fetal body dimensions, such as fetal liver length (FLL), could be considered as ultrasound parameters of glycemic control.[4,5] 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.[9–12]

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.[13,14] During this scan, fetal hyperinsulinemia may be suspected on the basis of increased fetal dimensions determined by the ultrasound examination. The abdominal circumference reflects the growth of insulin-sensitive organs, such as the fetal liver. Consequently, increased abdominal circumference measurements suggest excessive glycogen deposition in the liver secondary to raised fetal insulin levels. Such an association between fetal macrosomia and amniotic fluid insulin has already been documented in the third trimester and at birth,[15,16]

The aim of the present study was to test correlations between blood glucose levels during an oral glucose tolerance test (OGTT) with FLL evaluated the during mid-trimester ultrasound examination, as well to assess the value of these measurements in the screening of GDM in a high-risk population of pregnant women.

Methods

This prospective study was approved by the Research Ethics Committee of of Clinical Hospital Centre, Zemun–Belgrade (Belgrade, Serbia; no. 1636) and by the Research Ethics Committee of the Medical Faculty, University of Belgrade (no. 29/I-4). The study was performed at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia (Belgrade, Serbia) and at the Hospital for Gynaecology and Obstetrics, Clinical Hospital Centre, Zemun–Belgrade. The study population consisted of pregnant women at high risk of GDM who were undergoing a mid-trimester ultrasound examination. After informed consent had been obtained, a medical and obstetric history was obtained for all women who then underwent an obstetric ultrasound scan at 23 weeks gestation, followed by a fasting 3-h 100-g OGTT at 24 weeks gestation. Women were suitable for inclusion in the study if they had a singleton pregnancy, for which pregnancy duration was determined on the basis of the last certain menstrual period and confirmed by ultrasound measurement of fetal crown–rump length (at 10–12 weeks), and if they had risk factors for GDM (body mass index [BMI] >30 kg/m^2, multiparity, maternal age >35 years, previous delivery of a macrosomic child [>4000 g], polycystic ovary syndrome, family history of diabetes). Women with a multiple pregnancy, previous Cesarean sections, prepregnancy hypertension, prepregnancy pathological OGTT values, type 1 or 2 diabetes, aged <18 years, maternal–fetal blood group ABO incompatibility (titer >1: 30), on long-term medical treatment that may have affected glucose metabolism, and women with confirmed fetal abnormalities were excluded from the study.

Ultrasound examinations and measurements of the fetal liver were performed using either a variable convex transducer (2–6 MHz) of the Xario SSA-660A ultrasound machine (Toshiba Medical Systems, Tokyo, Japan) or the variable convex C2–61C transducer (2–6 Hz) of the Accuvix V10 ultrasound machine (Medison, Seoul, Korea). 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 hemidiaphragm to the tip of the right lobe.

The OGTT was performed using standard protocols. Briefly, after a 12-h overnight fast, venous plasma samples were collected to measure glucose levels at

fasting and then 1, 2 and 3 h after administration of a 100-g glucose load. The oral glucose load was administered chilled to minimize nausea, vomiting, and abdominal distension. Diagnoses of GDM were based on the criteria of the American Diabetes Association.[17]

Because the ultrasound examinations preceded the OGTT, all FLL measurements were made in a blinded manner with regard to the results of the OGTT. Furthermore, the people responsible for recruiting patients to the study, providing information about the study, obtaining medical and obstetric histories, scheduling ultrasound examinations and the OGTT (EG, EI, SD and UB) were not involved in performing the ultrasound examination. The physicians responsible for the ultrasound examinations (MP, MG, MK, TS, GK, BA and JR) were not informed about the data obtained previously for the study participants, which means they were blinded as to the risk group.

Statistical analysis

Data are presented as the mean ± SD. Categorical data are presented as absolute numbers with percentages and were analyzed using the Chi-squared test and Fisher's exact test. Continuous variables were analyzed using Student's *t*-test (normally distributed data) or the Mann–Whitney *U*-test (non-normally distributed data). Correlation analyses were performed using the Pearson product–moment correlation coefficient (normal distribution) and Spearman's rank correlation coefficient (non-normal distribution). Binary logistic regression was used to assess correlations between the FLL and GDM with adjustment for educational level, parity, and BMI. The ability of fetal liver measurements to discriminate between positive and negative OGTT was described by receiver operating characteristic (ROC) statistics using different cut-off levels of FLL. The area under the curve (AUC) was calculated and represents a quantitative measure of the predictive value of fetal liver measurements for a positive OGTT. Two-sided $P < 0.05$ was considered significant. The diagnostic efficiency of the established cut-off value of FLL was evaluated for sensitivity, specificity, positive predictive value, and negative predictive value. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL, USA).

Sample size calculation

To show the expected sensitivity of ultrasound FLL measurements (point estimate) ≥80% with a precision of 7%, it was calculated that the study needed to include 124 subjects.

Results

Three hundred and fifty-seven of 366 eligible pregnant women consented to participate in the study (between January 2012 and January 2013). Of the 357 women who consented to participate, nine were excluded because of an intolerance to the oral glucose load and a further 17 were excluded because they failed to show up for the OGTT, despite having provided consent and undergoing the ultrasound examination. This left a final study population of 331 women.

Descriptive characteristics of the study population are given in Table 1. The prevalence of GDM in this high-risk study population was 25.7%, with no significant differences in the demographic characteristics between subjects with and without GDM, except for BMI and secundiparity (which were significantly higher in women with GDM pregnancies) and a primary school level of education (which was significantly higher in non-GDM women; Table 1). Analysis of risk factors for GDM in the study population, as well as in the GDM and non-GDM subgroups, is presented in Table 2.

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; $R_0 = +0.47$, $R_{60} = +0.52$, $R_{120} = +0.58$, $R_{180} = 0.48$). Results of FLL measurements plotted against blood glucose levels immediately before and 60, 120 and 180 min after the 100-g glucose load OGTT are shown in Fig. 1. As indicated in Fig. 1, FLL increased with increasing blood glucose levels. Similar relationships between FLL and blood glucose levels were detected at all time points in the

Table 1 Characteristics of the study participants and fetal liver measurements

	GDM	Non-GDM	*P*-value
No. participants	85	246	NA
Age (years)	28.8 ± 4.9	28.9 ± 5.9	>0.05
BMI (kg/m^2)	29.7 ± 4.8	25.3 ± 3.9	<0.001
Parity			
Nulliparity	27 (31.76%)	103 (41.87%)	>0.05
Secundigravida	48 (56.47%)	109 (44.31%)	<0.05
Tercigravida	8 (9.42%)	22 (8.94%)	>0.05
Multiparity (≥4)	2 (2.35%)	12 (4.88%)	>0.05
Education			
Primary school level	5 (5.88%)	38 (15.45%)	<0.05
High school level	64 (75.29%)	178 (72.36%)	>0.05
University level	16 (18.83%)	30 (12.19%)	>0.05

Data are given as the mean ± SD or as the number of subjects in each group, with percentages in parentheses.
GDM, gestational diabetes mellitus.

Table 2 Prevalence of risk factors in the study group and subgroups

	Study group	GDM subgroup	Non-GDM subgroup
No. subjects	331 (100%)	85 (100%)	246 (100%)
Cumulative no. risk factors*			
One	196 (59.21%)	31 (36.47%)	165 (67.07%)
Two	114 (34.44%)	34 (40.00%)	80 (32.52%)
Three or more	21 (6.35%)	20 (23.53%)	1 (0.41%)
Type of risk factor†			
BMI >30 kg/m^2	81 (24.47%)	45 (52.94%)	36 (14.63%)
Multiparity	14 (4.23%)	2 (2.35%)	12 (4.88%)
Maternal age >35 years	85 (25.68%)	25 (29.41%)	59 (23.98%)
Delivery of macrosomic baby	101 (30.51%)	29 (34.18%)	73 (29.67%)
Polycystic ovary syndrome	65 (19.64%)	19 (22.35%)	46 (18.69%)
Family history of diabetes	143 (43.20%)	39 (45.88%)	104 (42.28%)
No. identified risk factors	489	159	330
Mean no. risk factors per person	1.48	1.87	1.34

*Data show the number of subjects in each group, with percentages in parentheses.
†Data show the number of subjects in each group with the risk factor, with the prevalence of the risk factors in each group or subgroup given in parentheses.
GDM, gestational diabetes mellitus; BMI, body mass index.

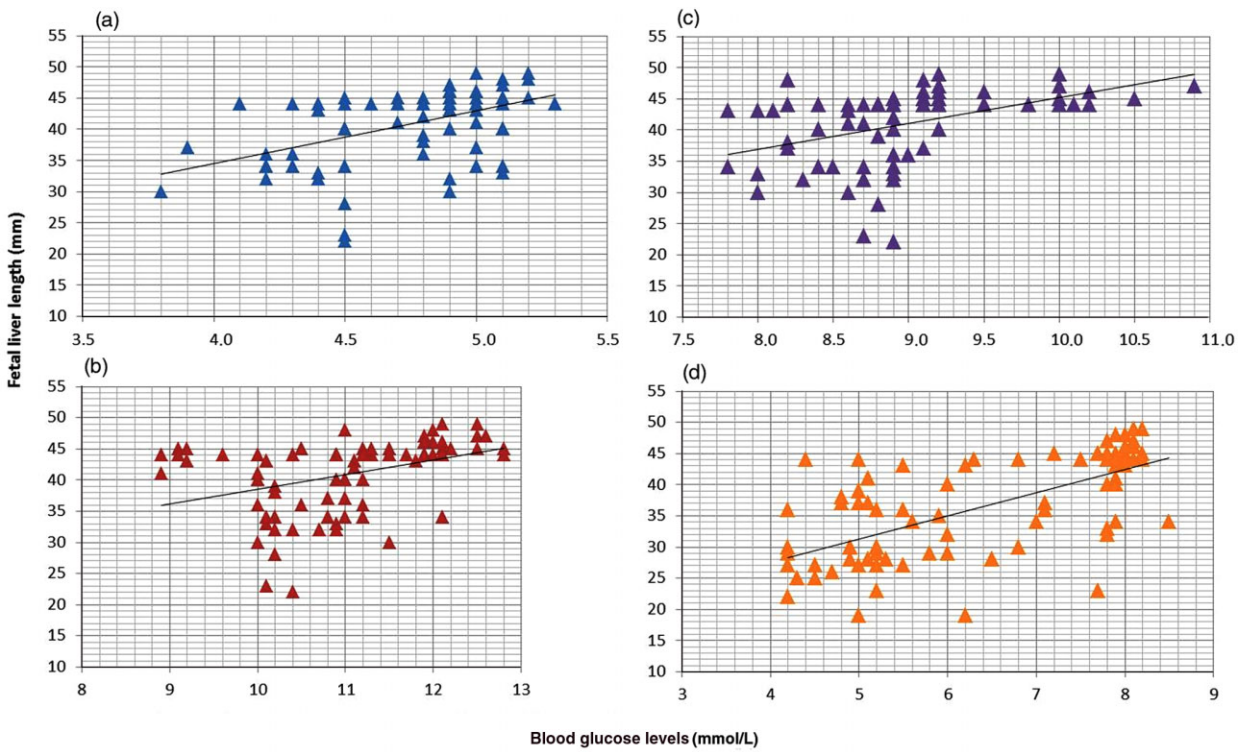

Figure 1 Fetal liver length (determined by ultrasound examination at 23 weeks gestation) plotted against blood glucose levels (a) immediately before and (b) 60, (c) 120 and (d) 180 min after a 100-g glucose load as part of an oral glucose tolerance test performed at 24 weeks gestation.

OGTT. Conversely, no such correlations were detected in non-GDM subjects ($P > 0.05$; $R_0 = +0.13$, $R_{60} = +0.07$, $R_{120} = +0.06$, $R_{180} = 0.04$).

Univariate analysis revealed significant differences between the GDM and non-GDM groups in BMI, primary school education, and secundiparity. Correlation analysis revealed that there was a significant correlation between FLL and BMI only ($r = 0.586$; $P < 0.001$), and not between FLL and either primary school educational level or parity.

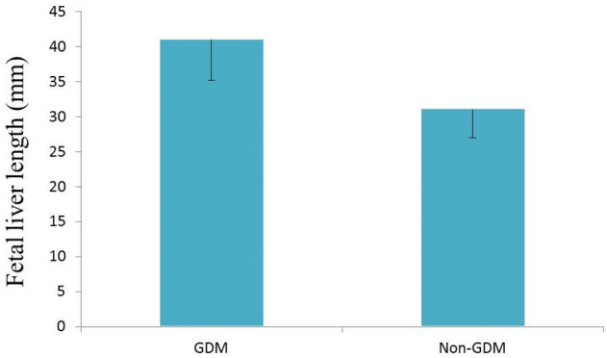

Figure 2 Fetal liver length in the gestational diabetes mellitus (GDM) and non-GDM groups.

Table 3 Diagnostic performance of fetal liver length measurement in predicting gestational diabetes mellitus

	%	95% CI
Sensitivity	71.76	61.0–81.0
Specificity	97.56	94.8–99.1
Positive predictive value	91.0	81.5–96.6
Negative predictive value	90.9	86.8–94.1
Area under the ROC curve	90.5	86.8–93.4

CI, confidence interval; ROC, receiver operating characteristic.

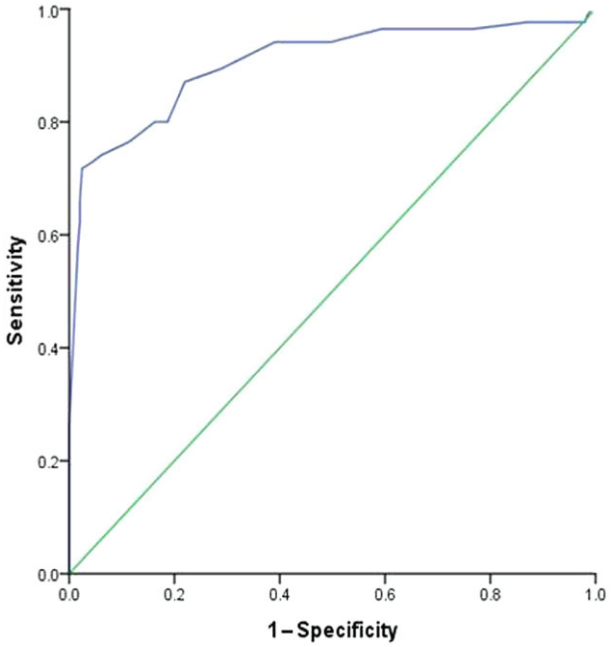

Figure 3 Ability of fetal liver measurements to discriminate between positive and negative oral glucose tolerance tests, as described by receiver operating characteristic (ROC) curve (blue line) statistics using different cut-off levels of fetal liver length.

A multivariate logistic regression model was created in three steps. In the first step, only liver length was used as an independent variable, with GDM as the dependent variable. A significant association was confirmed between FLL and GDM (odds ratio [OR] = 1.401; 95% confidence interval [CI] 1.308–1.501; $P < 0.001$; $R^2 = 0.597$). Adjustment for BMI resulted in no significant changes to the relationship (OR = 1.396; 95% CI 1.290–1.510; $P < 0.001$; $R^2 = 0.597$). Similar results were obtained following adjustment for BMI, educational level and parity (OR = 1.400; 95% CI 1.209–1.519; $P < 0.001$; $R^2 = 0.612$). According to the results of the multivariate logistic regression, FLL is significantly correlated with GDM independent of BMI, educational level, and parity.

Fetal liver measurements in GDM patients were significantly higher than in healthy pregnant women ($P < 0.001$; Fig. 2).

The ROC analysis established a cut-off value for FLL of 39 mm for the prediction GDM, which has a sensitivity of 71.76%, specificity 97.56%, positive predictive value 91.0%, and negative predictive value 90.9%. When tested as a potential prognostic factor for GDM, fetal liver measurements showed excellent diagnostic performance (Table 3). The usefulness of FLL measurements was supported by a high AUC_{ROC} (90.5%). The ability of the cut-off value of 39 mm for FLL to discriminate between positive and negative OGTT described by the ROC statistics is shown in Fig. 3.

Discussion

The present study has demonstrated that there is a highly significant correlation between FLL and blood glucose values during an OGTT in patients with GDM. The nature of the relationship detected implies that FLL may be a strong predictive factor for OGTT values; this was confirmed by ROC analysis. Conversely, no such relationship was found in non-GDM pregnancies.

Ultrasound FLL measurements among the non-GDM subjects in the present study are in agreement with those reported by Vintzileos et al.[18] Furthermore, the significantly higher FLL measurements in GDM pregnancies compared with healthy pregnancies ($P < 0.001$) in the present study are in agreement the results of another study, in which two-dimensional ultrasound was used to determine liver size.[19] A possible explanation for the positive correlation detected in the present study may be that 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.[9,10,12]

The results of the present study indicate that there is a positive correlation between FLL and responses to the

OGTT before the test and at each of the three time points tested after glucose administration. The OGTT is, in fact, a kind of a physiological test, with blood glucose levels before the glucose load mimicking fasting blood glucose levels and blood glucose levels after the glucose load mimicking levels observed after routine carbohydrate intake. Bearing that in mind, the explanation for the observed correlation may be found in studies that have shown that maternal fasting and postprandial blood glucose levels in diabetic pregnancies are correlated with fetal size adjusted for birth weight or gestational age.[20,21] In addition, the results of previous clinical and experimental studies emphasize the ability of insulin to stimulate fetal growth and the growth of insulin-sensitive organs, confirming the hyperglycemia–hyperinsulinemia hypothesis. Fetal pancreatic β-cell function in pregnancies complicated by GDM is directly correlated with maternal glycemia, and fetal size is directly correlated with fetal insulin production during the second half of gestation.[22] Finally, some authors have reported that prolonged in utero administration of insulin in normal fetal monkeys caused substantial growth of fetal adipose tissue, liver, and heart in the absence of maternal hyperglycemia.[23] Furthermore, Naeye[24] reported that, in post-mortem specimens, the liver size of fetuses from diabetic mothers was increased by approximately 80% compared with normal controls because of both cellular hyperplasia and hypertrophy and an increased amount of hematopoietic tissue. This abnormal growth is mostly attributable to fetal hyperinsulinemia.[25]

Although the relationship between FLL and maternal blood glucose levels during the OGTT appears to be straightforward, there are several differences between the GDM and non-GDM subjects that need to be discussed before final conclusions can be drawn. Specifically, we found significant differences in the BMI of these two groups. Although this result was expected, given that BMI is one of the strongest predictors of GDM, it could be of great importance in interpretation of the results, particularly in light of the outcomes of our previous study,[26] in which we investigated the association between maternal BMI and ultrasound FLL measurements. The results of that study indicated that maternal BMI was positively correlated with FLL in the GDM and non-GDM populations,[26] although this correlation was stronger in GDM subjects. Therefore, we controlled for this potential confounder in the present study by using the moderator model. However, after adjustment for BMI, no significant changes were obtained for FLL. According to the results of the multivariate logistic regression, liver length is significantly associated with GDM independent of BMI. Similar results were obtained for FLL after adjusting for BMI, primary school level education, and secundiparity, meaning that adjustment for potential confounders does not result in a loss of significance for the established correlation.

The results regarding the significant difference between the prevalence of a low level of education in the GDM and non-GDM groups is surprising. There were more women with a primary school level of education in the non-GDM group. Even though low socioeconomic status has been shown to contribute to the risk of developing type 2 diabetes, the relationship between GDM and socioeconomic category is less recognized, with contradictory results observed in previous studies.[27,28] Furthermore, little is known about the possible relationship between maternal educational level, as one of the determinants of socioeconomic status, and GDM. Most probably in our population there was no direct effect of low maternal educational level on the increased occurrence of GDM, which is consistent with the results of Bertolotto et al.,[27] but in contrast with the findings reported by Hedderson et al.[28] Although the present study does not address this issue, we think that further research concerning this subject would be of importance for inclusion or exclusion of low education level as a risk factor for GDM.

In the second part of the study we investigated the clinical applicability of the observed correlation and, to the best of our knowledge, this is the first study to evaluate ultrasound measurements of FLL as a tool for the prediction of gestational diabetes. We demonstrated that fetal liver measurements during the mid-trimester ultrasound examination can be used to predict GDM in a high-risk population. Although it has been shown that fetal liver dimensions have a role in identifying fetal growth acceleration in diabetic pregnancies, the previous studies addressed patients with insulin-dependent diabetes mellitus rather than GDM,[29] or did not deal with the diagnostic value of these findings.[30] In the study of Boito et al.,[29] liver volumes were evaluated by three-dimensional ultrasonography. Although probably more accurate in the evaluation of fetal liver dimensions, this method is not part of routine pregnancy monitoring, in contrast with two-dimensional ultrasonography, which was used in the present study.

Use of the GCT is routinely associated with a sensitivity and specificity of 80% and 90%, respectively, but positive and negative predictive values fluctuate according to the prevalence of GDM in the population tested.[31] Therefore, approximately 20% of patients remain undiagnosed, even with universal screening. In a recent review regarding GDM screening tests, it was suggested that the GCT has a relatively low sensitivity and reproducibility.[32] This could be explained by the fact that the

GCT results in patients are significantly influenced by the timing since the last meal. Lewis et al. reported that up to 73% of the population had their test less than 2 h postprandially. Exposure to carbohydrates (i.e. the meal) immediately before the glucose load of the test may result in enhanced insulin sensitivity and glucose disposal to the tissues, which may significantly reduce test sensitivity (the Staub–Traugott effect).[33] It is important to stress that, unlike in the GCT, this phenomenon does not influence fetal liver measurements determined by ultrasound examination.

The idea of alternative GDM detection with fetal liver measurements during routine mid-trimester ultrasound examination arose from previous studies in which we demonstrated that GDM could be detected by third-trimester ultrasound examinations,[4,5] as well as other studies in which earlier screening for the disease was recommended. Nahum et al.[34] suggested that the ideal period to screen for GDM in high-risk groups is around 16 weeks gestation because of the embryological development of fetal β-cells. Each islet cell functions as an endocrine organ and differentiates between Weeks 10 and 12 of gestation. The cells recognize and respond to maternal blood glucose before 15 weeks gestation, suggesting that metabolic perturbations take place before the diagnosis and that earlier screening and intervention may be needed.[35]

In the present study we used ROC analysis to make a decision regarding the cut-off value for FLL in predicting GDM. With regard to the cut-off value of 39 mm established herein, excellent parameters of validity were demonstrated, with a sensitivity and specificity of 71.76% and 97.56% respectively, and positive and negative predictive values of 91.0% and 90.9%, respectively. The value of these findings is reflected in the fact that, in the present study, the GDM diagnosis was made earlier than usual, which is normally between 24 and 28 weeks gestation. This is particularly important bearing in mind that the prevalence of the disease increases with pregnancy progression. Seshian et al.[36] reported that 22.4% of pregnant women had glucose intolerance between 17 and 23 weeks gestation, compared with up to 61.3% after 24 weeks. The usefulness of FLL measurements was supported by a high AUC (90.5%) during ROC analysis.

One of the major disadvantages of many of the screening tests used currently is false-positive results. In the present study, fetal liver measurements demonstrated better specificity than GCT results based on data in the literature.[31] It is important to stress that, when used in low-prevalence settings, even excellent tests may have poor positive predictive values. Our sample included only women at a high-risk of GDM, which means that every woman had at least one risk factor for GDM, but most had a combination of two or more risk factors at the same time. The prevalence of GDM in our population was relatively high (25.7%), which is in accordance with the results reported by Moses et al.,[37] who reported that the prevalence of GDM in the high-risk population ranged from 8.5% (among women with only one and the weakest risk factor for GDM) to 60.8% (among women who had a combination of risk factors). High prevalence of the disease in high-risk pregnant women validates the use of a mid-trimester ultrasound FLL measurement to detect GDM in a two-step diagnostic approach based on routine examinations that are performed as part of pregnancy monitoring in many countries.

Selection of the high-risk population in the present study was based only on those factors that are well known, clearly defined, universally recognized, and applied in the identification of high-risk populations worldwide. Accordingly we surveyed pregnant women representative of the screening population as a whole, and the survey respondents included relevant groups from the wider population (general population of pregnant women). Therefore, the study sample represents the population of interest, which is important in terms of generalizability of the sample, and the results could be applied in other countries where risk factor-based screening is performed.

Furthermore, the strategy of screening with the GCT at 24–28 weeks gestation may not always be a feasible option in all circumstances because of organizational reasons and oversights. Even in countries with well-developed healthcare systems, despite numerous recommendations for GCT screening stipulated in local guidelines, only one in three pregnant women with risk factors has been tested using the GCT.[38] In contrast, the mid-trimester ultrasound examination is performed in almost all pregnant women. Therefore, 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. Furthermore, the GCT is usually performed between 24 and 28 weeks gestation. Earlier detection of GDM with a mid-trimester ultrasound examination may prolong the time during which a metabolic intervention could be instituted.

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. However, the present study was conducted in pregnant women at 23 weeks gestation. Mid-trimester scans are usually performed from 18 to 23 weeks gestation. Therefore, the findings of the study are not applicable in all mid-trimester ultrasound patients.

Bearing in mind that the effects of impaired maternal glucose metabolism on the fetal liver need time to manifest themselves, further studies are needed to confirm or to refute our findings at earlier than 23 weeks gestation. Furthermore, as pregnancy progresses, it is known that there is an increasing likelihood of developing GDM, which implies that it is likely that affected individuals will be missed if the screening test is performed early in pregnancy. Consequently, using liver measurements made during the mid-trimester, we would not be able to detect patients in whom the disease appears during the third trimester.

The size of our study population was relatively large and sufficiently powered to observe associations. We were also very careful in statistical analyses and considered relevant multivariate models for consistency of findings. These facts could be considered as strengths of the study. One limitation of the study could be the absence of any follow-up. Such monitoring after the first, second and finally third trimester could enable comparison of the number of women who would be affected by GDM in each trimester. That way the best timing for early detection of GDM could be determined exactly. Furthermore, evaluation of the outcome of pregnancy and clinical characteristics of a newborn would confirm or refute more reliably the findings we have detected in utero in order to verify our conclusions.

In conclusion, in the present study we detected a strong positive correlation between ultrasound FLL and OGTT values in GDM patients. The results of ROC analysis indicate that FLL may even be a strong predictor of GDM. This could imply that fetal liver measurement may be an important addition to conventional methods in the future early detection of GDM.

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Disclosure

The authors have no conflicts of interest to declare.

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