

Does detection of a large for gestational age (LGA) fetus in fetal anomaly scan (FAS) require an early oral glucose screening test (OGTT) and can LGA fetus be detected at birth?

B. BAYRAKTAR^{1,2}, H. GOLBASİ³, C. GOLBASİ⁴, O.B. CEGİLLİ¹, B. SEVER³, T. VURAL¹, M.G. BAYRAKTAR¹, G. TOKLU¹, C.E. TANER³

¹Department of Obstetrics and Gynecology, University of Health Sciences, Tepecik Training and Research Hospital, Izmir, Turkey

²Department of Obstetrics and Gynecology, Division of Perinatology, Ankara Etlik City Hospital, Ankara, Turkey

³Department of Obstetrics and Gynecology, Division of Perinatology, University of Health Sciences, Tepecik Training and Research Hospital, Izmir, Turkey

⁴Department of Obstetrics and Gynecology, Faculty of Medicine, Tinaztepe University, Izmir, Turkey

Abstract. – OBJECTIVE: Gestational diabetes mellitus (GDM) complications increase with late diagnosis and late treatment, so early diagnosis and treatment is one of the most important factors in preventing complications. We tried to find an answer to the question of whether the detection of large for gestational age (LGA) fetus in fetal anomaly scan (FAS) requires earlier oral glucose screening test (OGTT) and predicts LGA fetus at birth.

PATIENTS AND METHODS: Pregnant women who underwent fetal anomaly scan and gestational diabetes screening at the Department of Obstetrics and Gynecology, University of Health Sciences, Tepecik Training and Research Hospital between 2018 and 2020 were included in this large retrospective cohort study. FAS was routinely performed between 18-22 weeks in our hospital. 75 grams of OGTT was used for gestational diabetes screening and it was performed between 24-28 weeks.

RESULTS: This large retrospective cohort study was performed on 3,180 fetuses, 2,904 appropriate for gestational age (AGA) and 276 LGA, in the second trimester. The prevalence of GDM was significantly higher in the LGA group (OR 2.44, 95% CI 1.66-3.58; $p < 0.001$). Insulin requirement for blood glucose regulation was significantly higher in the LGA group (OR 3.6, 95% CI 1.68-7.7; $p = 0.001$). Fasting and 1st hour OGTT values were similar between the groups, but 2nd hour OGTT values were significantly higher in the second trimester LGA group ($p = 0.041$). The prevalence of LGA newborns at birth was higher in second trimester LGA fetuses than in fetuses with AGA (21.1% vs. 7.1%, $p < 0.001$).

CONCLUSIONS: The fact that the estimated fetal weight (EFW) measured in the second trimester FAS is LGA may be related to GDM in the future and LGA fetus at birth. A more detailed GDM risk questioning should be performed to these mothers and OGTT should be considered when additional risk factors are detected. In addition to all these, glucose regulation may not be possible with diet alone in mothers who have LGA in the second trimester ultrasound and who may have GDM in the future. These mothers should be monitored more closely and more carefully.

Key Words:

Gestational diabetes, Fetal anomaly scan, Anthropometry, Birth time, Pregnancy outcome.

Introduction

One of the most common complications of pregnancy is gestational diabetes mellitus (GDM), which is defined as varying degrees of glucose intolerance that initially begins during pregnancy¹. The prevalence of GDM worldwide is between 1% and 45% (mean, 7-10%)^{2,3}. In Turkey, its prevalence varies between 1.9% and 27.9% (mean, 7.7%) based on different regions⁴. GDM increases the risk of preeclampsia, polyhydramnios, and urinary infections. Additionally, it increases the risk of abortion, preterm birth, congenital anomaly, intrauterine fetal death, large for gestational

age (LGA) and macrosomia, related shoulder dystocia, and operative delivery^{1,5-7}. In addition, GDM is associated with polycystic ovary syndrome assisted reproductive techniques pregnancies, and insulin resistance⁸⁻¹⁰. It has been shown¹¹ that pre-pregnancy medical treatments can be beneficial in preventing GDM and related adverse perinatal outcomes in these patients. Thus, major institutions and organizations recommend all pregnant women to be routinely screened with an oral glucose screening test (OGTT) between 24 and 28 weeks^{1,12,13}.

Fetal anomaly scan (FAS), also known as mid-pregnancy or anomaly scan, is one of the most important scans during pregnancy that is performed in the second trimester. Currently, many large institutions and organizations recommend FAS at 18-22 weeks^{14,15}. Moreover, fetal biometry and estimated fetal weight (EFW) are routine measurements checked during this scan¹⁴⁻¹⁶.

GDM complications increase with late diagnosis and late treatment; hence, early diagnosis and treatment are important factors that could prevent complications^{5,7}. OGTT is performed between 24 and 28 weeks. Some factors are thought to predict fetal growth and GDM before 24 weeks^{17,18}. Considering that GDM affects fetal weight, second trimester EFW may also be one of these factors. Therefore, we aimed to investigate whether detection of LGA fetuses in FAS requires earlier OGTT and predicts GDM.

Patients and Methods

Study Design

This study included pregnant women who underwent FAS and GDM screening at the Department of Obstetrics and Gynecology, University of Health Sciences, Tepecik Training and Research Hospital between 2018 and 2020. FAS was performed in our hospital between 18 and 22 weeks following the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines¹⁵. Fetal biometry and EFW measurements were also obtained during the ultrasonographic scan. In our hospital, 75 g OGTT was used for GDM screening and performed between 24 and 28 weeks. According to the criteria of The International Association of Diabetes and Pregnancy Study Groups, OGTT is considered positive for pregnant women with at least one measurement value of ≥ 92 mg/dL for fasting, 180 mg/dL for

the first hour, and 153 mg/dL for the second hour. Pregnant women without any positive values were considered normoglycemic¹³.

Second-trimester EFW was calculated using the Hadlock 3 formula [$10^{(1.326-0.00326 \times AC \times FL + 0.0107 \times HC + 0.0438 \times AC + 0.158 \times FL)}$] (g, cm)] using abdominal circumference (AC), femur length (FL), and head circumference (HC)¹⁹. Large-scale studies^{20,21} showed that this formula provides the best estimates of fetal weight in the evaluation of fetuses, including fetuses suspected of being small or large, and the ISUOG recommends using this formula. The Eunice Kennedy Shriver National Institute of Child Health and Human Development growth chart was used for percentile calculation²².

This study was conducted following the Helsinki Declaration Ethical Standards. The University of Health Sciences Tepecik Education and Research Hospital Local Ethics Committee (approval number: 2020/9-10) approved this study.

Study Participants

The inclusion criteria were singleton pregnancies and term (≥ 37 weeks, < 42 weeks) pregnant women who delivered in our hospital. We excluded fetuses with major or minor fetal anomalies, pregnant women with thyroid disease, pregnant women with known type 1 and type 2 diabetes, pregnancies with gestational hypertension/preeclampsia, pregnant women with metabolic disease, pregnant women using medication, pregnant women with fetal growth restriction, incomplete records, and/or whose records could not be obtained.

Based on EFW and AC, fetuses on $> 10^{\text{th}}$ to $< 90^{\text{th}}$ percentile and fetuses on $\geq 90^{\text{th}}$ percentile were classified as appropriate for gestational age (AGA) and LGA in the second trimester, respectively²³. Similarly, fetuses on the $> 10^{\text{th}}$ and $< 90^{\text{th}}$ percentile and those on the $\geq 90^{\text{th}}$ percentile based on birth weight were classified as AGA and LGA, respectively.

Statistical Analysis

Statistical Package for the Social Sciences version 26.0 (IBM Corp., Armonk, NY, USA) was used for data analysis, and the significance level was $p < .05$ for all analyses. The Shapiro-Wilk test was used to determine data distribution. Student's *t*-test was used for normally distributed data in comparison of the groups, and the data were presented as mean \pm SD. The Mann-Whitney U test was used to compare the data not showing

Table I. Maternal, obstetric and neonatal characteristics of the study participants.

	AGA at 2 nd trimester n = 2,904	LGA at 2 nd trimester n = 276	p
Maternal age (year) (mean ± SD)	29.48 ± 6.11	30.78 ± 5.65	< 0.001
Parity (n,%)			< 0.001
Nulliparous	1,032 (35.5%)	60 (21.7%)	
Multiparous	1,872 (64.5%)	216 (78.3%)	
Pre-pregnancy BMI (kg/m ²) (mean ± SD)	23.1 ± 2.8	23.8 ± 3.2	0.435
EFW at second trimester (g) (mean ± SD)	344.98 ± 120.18	384.91 ± 97.97	0.008
EFW percentile at second trimester (%) (mean ± SD)	51.55 ± 19.87	91.14 ± 5.54	< 0.001
AC at second trimester (mm) (mean ± SD)	155.28 ± 17.60	162.11 ± 15.01	< 0.001
AC percentile at second trimester (%) (mean ± SD)	50.95 ± 21.52	91.36 ± 12.89	< 0.001
Gestational age at delivery (week) (mean ± SD)	39.13 ± 1.09	38.68 ± 1.14	0.105
Gender (n,%)			0.543
Male prevalence	1,428 (49.2%)	141 (51%)	
Female prevalence	1,476 (50.8%)	135 (49%)	
Birth weight (g) (mean ± SD)	3,265.45 ± 407.55	3,564.57 ± 564.04	< 0.001
APGAR Score (n,%)			
< 7 at 1 st minute	156 (5.4%)	12 (4.4%)	0.467
< 7 at 5 th minute	36 (1.2%)	1 (0.4%)	0.194

AGA: Appropriate for gestational age, LGA: Large for gestational age, BMI: Body mass index, EFW: Estimated fetal weight. AC: Abdominal circumference.

normal distribution, and the data were presented as median ± (min, max). The Chi-square test was used to compare categorical variables, and the odds ratio [OR, 95% Confidence Interval (CI)] was calculated.

Results

This large retrospective cohort study was performed on 3,180 fetuses, including 2,904 AGA and 276 LGA, in the second trimester. Table I shows the maternal, obstetric, and neonatal outcomes. In the LGA group, maternal age was older, and multiparity was more common ($p < 0.001$ and $p < 0.001$, respectively). Both groups were similar in pre-pregnancy body mass index (BMI), gestational age at delivery, and fetal sex. The

second-trimester AC (155.28 ± 17.60 vs. 162.11 ± 15.01), EFW (344.98 ± 120.18 vs. 384.91 ± 97.97), AC percentile (50.95 ± 21.52 vs. 91.36 ± 12.89), and EFW percentile (51.55 ± 19.87 vs. 91.14 ± 5.54) were higher in the LGA group ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Similarly, birth weight was $3,564.57 \pm 564.04$ and $3,265.45 \pm 407.55$ in the LGA and AGA groups, respectively, which was significantly different ($p < 0.001$). No significant difference was observed between groups in the 1st and 5th-minute appearance, pulse, grimace, activity and respiration (APGAR) scores of newborns < 7 (Table I).

LGA fetuses in the second trimester were divided into two groups; those with and without GDM and were compared in Table II in terms of maternal factors. Accordingly, maternal age was older in the GDM group (36.33 ± 1.72 vs. 29.95

Table II. Maternal factors among fetuses with LGA in the second trimester with and without GDM.

	Not develop GDM after LGA at 2 nd trimester n = 240	Develop GDM after LGA at 2 nd trimester n = 36	p
Maternal age (year) (mean ± SD)	29.95 ± 5.57	36.33 ± 1.72	< 0.001
Pre-pregnancy BMI (kg/m ²) (mean ± SD)	23.2 ± 2.4	25.8 ± 1.2	0.001
Parity (n%)			0.003
Nulliparous	59 (24.6%)	1 (2.8%)	
Multiparous	181 (74.4%)	35 (97.2%)	
BMI at delivery (kg/m ²) (mean ± SD)	30.2 ± 2.7	33 ± 3.3	0.002

GDM: Gestational diabetes mellitus, LGA: Large for gestational age, BMI: Body mass index.

Table III. Maternal factors of AGA and LGA at birth among fetuses with LGA in the second trimester.

	AGA at birth n = 248	LGA at birth n = 48	p
Maternal age (year) (mean \pm SD)	30.42 \pm 5.93	32.50 \pm 3.67	0.020
Pre-pregnancy BMI (kg/m ²) (mean \pm SD)	23.4 \pm 2.4	24 \pm 2.7	0.039
Parity (n, %)			0.546
Nulliparous	48 (21.1%)	12 (25%)	
Multiparous	180 (78.9%)	36 (75%)	
BMI at delivery (kg/m ²) (mean \pm SD)	30.1 \pm 2.4	31.9 \pm 2.3	0.041

AGA: Appropriate for gestational age, LGA: Large for gestational age, BMI: Body mass index.

\pm 5.57, $p < 0.001$). Pre-pregnancy BMI was 23.1 \pm 2.4 and 25.9 \pm 1.2 in the group without and with GDM, respectively, which was significantly different ($p = 0.001$). Similarly, BMI at delivery was higher in the group with GDM (30.2 \pm 2.7 vs. 33 \pm 3.3, $p = 0.002$). Moreover, multiparity was more common in the group with GDM ($p = 0.003$) (Table II).

LGA fetuses in the second trimester were divided into pregnancies with AGA and LGA at delivery and analyzed in Table III according to maternal factors. Accordingly, maternal age was older in the group with LGA at birth (30.42 \pm 5.93 vs. 32.50 \pm 3.67, $p < 0.020$). Pre-pregnancy BMI and BMI at delivery were significantly higher in the group with LGA at birth (23.4 \pm 2.4 vs. 24 \pm 2.7, $p = 0.039$ and 30.1 \pm 2.4 vs. 31.9 \pm 2.3, $p = 0.041$). The parities between groups were similar (Table III).

AGA and LGA fetuses in the second trimester were analyzed in Table IV for the development of GDM. The prevalence of GDM was significantly higher in the LGA group (OR, 2.44; 95% CI, 1.66-3.58; $p < 0.001$). Insulin requirement for blood glucose regulation was significantly higher in the LGA group (OR,

3.6; 95% CI, 1.68-7.7; $p = 0.001$). Fasting and 1st-hour OGTT values were similar between the groups, but 2nd-hour OGTT values were significantly higher in the second trimester LGA group ($p = 0.041$). The prevalence of LGA newborns at birth was higher in second trimester LGA fetuses than in those with AGA (21.1% vs. 7.1%, $p < 0.001$) (Table IV).

Discussion

Pregnancies complicated by diabetes are risky pregnancies requiring close follow-up from both maternal and fetal aspects. The multicenter and prospective hyperglycemia and adverse pregnancy outcomes study⁵ revealed a significant relationship between maternal hyperglycemia and poor infant outcomes, such as macrosomia, shoulder dystocia, hyperinsulinemia, neonatal hypoglycemia, respiratory distress syndrome, cesarean delivery, and even fetal death. Recently, these negative effects were not limited to pregnancy, and it was discovered^{24,25} that GDM may play a role in childhood obesity. Thus, international organizations recommend GDM screening with

Table IV. Evaluation of pregnancies with AGA and LGA in the second trimester in terms of development of gestational diabetes.

	AGA at 2 nd trimester n = 2,904	LGA at 2 nd trimester n = 276	OR 95% CI*	p
GDM prevalence (%)	168/2,904 (5.8%)	36/276 (13%)	2.44 (1.66-3.58)	< 0.001
GDMs regulated by diet (%)	108/168 (64.3%)	12/36 (33.3%)	0.27 (0.13-0.59)	< 0.001
GDMs treated with insulin (%)	60/168 (35.7%)	24/36 (66.7%)	3.6 (1.68-7.7)	0.001
Fasting (mg/dL) (median, min-max)	82 (61-115)	79 (66-141)	-	0.228
Hour 1 (mg/dL) (median, min-max)	132 (51-165)	128 (73-286)	-	0.483
Hour 2 (mg/dL) (median, min-max)	104 (49-226)	107 (75-155)	-	0.041
LGA at birth (%)	180/2,904 (7.1%)	48/276 (21.1%)	3.47 (2.44-4.93)	< 0.001

*LGA at 2nd trimester groups were taken as reference group. AGA: Appropriate for gestational age, LGA: Large for gestational age, GDM: Gestational diabetes mellitus.

OGTT at 24-28 weeks of pregnancy²⁶. OGTT can be performed in the first trimester in the presence of various risk factors, which are extremely limited. Early prediction of GDM is extremely important to prevent complications and initiate early treatment. Additionally, FAS can be performed earlier than OGTT, and many large institutions and organizations recommend performing it at 18-22 weeks. In this scan, AC and EFW values were measured routinely. A fetus determined to be LGA at this time can be considered risky, and further evaluation is warranted.

The development of GDM was observed to be approximately 2.44 times more frequent in the second trimester LGA group compared with the AGA group (OR, 2.44; 95% CI, 1.66-3.58; $p < 0.001$). Studies on this subject in the literature are limited. The study of Liao et al¹⁸ reported no significant relationship between second trimester EFW measurement and the development of GDM, whereas that of Rekawek et al²⁷ found the prevalence of GDM to be higher in the second trimester LGA group, similar to our study. Both Liao et al¹⁸ and Rekawek et al²³ found a significant relationship between second trimester EFW and birth weight, similar to our study. Studies in literature agree on predicting LGA fetuses but differ in terms of GDM prevalence. Moreover, an important difference between study designs is the ethnicity since it is a parameter that affects fetal development and newborn weight, and the use of population-based growth charts is recommended²⁸. However, the inadequacy of population-based growth curves leads to the use of international growth curves. This situation affects the real AGA and LGA ratio in every society and changes their prevalence. Compared with both our study and a study by Rekawek et al²⁷, Liao et al¹⁸ had a lower sample size, and this may have affected the level of significance. Unlike both studies^{18,27}, we compared the second trimester EFW of diabetic patients who were followed-up only with diet and needed insulin in addition to diet, and the insulin requirement was approximately 3.6 times higher in the second trimester LGA group (OR, 3.6; 95% CI, 1.68-7.7; $p = 0.001$). Therefore, an LGA fetus in the second trimester increases not only the prevalence of GDM but also insulin requirement.

LGA newborn is associated with increased maternal age and multiparity^{29,30}. We observed older maternal age and multiparity more frequently in the second trimester LGA group. Similar to LGA, GDM is also associated with increasing age and

parity^{31,32}. Additionally, in this study, maternal age was older in LGA newborns in the second trimester LGA group, but the parities were similar in AGA and LGA newborns. The loss of function of pancreatic B cells and increased insulin resistance with age are factors that play a role in the development of diabetes and GDM³³. Moreover, multiparous women consume high calories and have a more sedentary lifestyle, and inflammation is known to increase with parity³⁴. In our study, maternal age and multiparity were higher in the second trimester LGA group who developed GDM compared to those who did not.

Pre-pregnancy BMI and weight gain during pregnancy are important factors in fetal growth and perinatal outcomes^{35,36}. Maternal obesity, being underweight, and inadequate weight gain are associated with poor perinatal outcomes³⁵. Both high pre-pregnancy BMI and high pregnancy weight gain are independent risk factors for LGA and/or GDM^{37,38}. No significant difference was found between maternal pre-pregnancy BMIs in pregnancies with AGA and LGA in the second trimester. However, both pre-pregnancy and delivery BMI were significantly higher in pregnant women who developed GDM in the later period. In addition, BMI values were significantly lower in mothers of second-trimester fetuses who were delivered AGA. Our results are consistent with the idea that high maternal BMI in the pre-pregnancy period and high weight gain during pregnancy increase the risk of GDM and LGA newborns due to dense adipose tissue and insulin resistance^{35,38}.

Limitations

This study had some limitations. Because this is a retrospective study, factors affecting fetal growth, such as socioeconomic status and cigarette and alcohol use, were not considered. We also used international curves similar to other studies because we could not find a current and reliable population-based growth curve. Our strengths include the calculation of all percentile values transparently based on numerical measurements and using a large sample. Thus, our results are valuable despite our limitations.

Conclusions

EFW determined as LGA in the second-trimester FAS should alert us to GDM. A more detailed GDM risk questioning should be per-

formed on mothers, and OGTT should be considered when additional risk factors are detected. In addition, glucose regulation may not be possible with diet alone in mothers with LGA fetuses in the second-trimester ultrasound and who may develop GDM. These mothers should be monitored more closely and carefully.

Conflict of Interest

The authors declare that they have no conflict of interests.

Funding

The authors received no funding for this work.

Ethics Approval

This study was conducted following the Ethical Standards of the Helsinki Declaration. The University of Health Sciences, Tepecik Education and Research Hospital Local Ethics Committee (approval number: 2020/9-10) approved this study.

Informed Consent

Not applicable.

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