Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1520019

Prediction of gestational diabetes mellitus risk in early pregnancy using antenatal screening biomarkers

Antenatal tarama biyobelirteçleri kullanılarak erken gebelikte gestasyonel diabetes mellitus riskinin tahmin edilmesi

Gul Boran SARIOGLU[1*], Emre Erdem TAS[2*]

[1]Gölbaşı Şehit Ahmet Özsoy Devlet Hastanesi, Kadın Doğum Kliniği, Ankara, Turkey
[2]Ankara Yıldırım Beyazıt Üniversitesi Kadın Hastalıkları ve Doğum ABD, Ankara Bilkent Şehir Hastanesi Kadın Doğum Kulesi, Ankara, Turkey

Yazarlar Gül Boran SARIOGLU ve Emre Erdem TAS bu çalışmaya eşit katkıda bulunmuştur ve eş yazarlardır.

ABSTRACT

Aim: In this study, we aimed to compare their success in predicting the risk of Gestational Diabetes Mellitus (GDM) using demographic (age, gravidity, parity), body mass index (BMI), first-trimester fasting blood glucose (FBG), thyroid-stimulating hormone (TSH), and antenatal screening biomarkers (dual and quadruple tests).

Materials and Methods: In this study, 800 pregnant women who underwent a one-step 75 g Oral Glucose Tolerance Test (OGTT) and antenatal screening tests at a tertiary hospital between January 2017 and June 2020 were retrospectively investigated. After patients were divided into two groups based on their GDM screening test results, the examined parameters were compared between the GDM-Positive and GDM-Negative groups. Once the parameters significantly associated with GDM were determined, their clinical utility in the early diagnosis of GDM was investigated.

Results: GDM was diagnosed in 159 (19.8%) of 800 patients. The GDM-Positive group had a higher age, gravidity, parity, BMI, and first-trimester serum FBG levels, as well as lower serum PAPP-A MoM levels than the GDM-Negative group (P <0.05). There were no significant differences between the groups based on serum TSH and f-βhCG, NT, AFP, uE3, ßhCG, and Inhibin-A MoM levels. Binary logistic regression analysis revealed that increased age (P=0.02, CI=1.007-1.096, OR=1.050), BMI (P<0.01, CI=1.452-3.213, OR=1.107), and first-trimester serum FBG levels were independently associated with GDM.

Conclusion: The use of first- and second-trimester antenatal screening tests for predicting GDM risk does not appear meaningful. Further studies are needed to determine the usability of these tests for early diagnosis of GDM in the Turkish population.

Keywords: Gestational diabetes mellitus, antenatal screening, risk assessment

ÖZ

Amaç: Bu çalışmada demografik veriler (yasş, gravida, parite), vücut kitle indeksi (VKİ), ilk-trimester açlık kan şekeri (AKŞ), tiroid uyarıcı hormon (TSH) ve antenatal tarama test biyobelirteçlerinin (ikili ve dörtlü tarama) Gestasyonel Diabetes Mellitus (GDM) riskini öngörmedeki başarılarını karşılaştırması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada Ocak 2017 – Haziran 2020 tarihleri arasında üçüncü basamak bir hastanede tek-basamak 75 gr Oral Glukoz Tolerans Testi (OGTT) ve antenatal tarama testleri yapılan 800 gebe retrospektif olarak incelendi. Olgular GDM tarama sonuçlarına göre iki gruba ayrıldıktan sonra GDM-Pozitif ve GDM-Negatif gruplar incelenen parametreler açısından karşılaştırıldı. GDM ile anlamlı derecede ilişkili parametreler belirlendikten sonra bunların GDM'nin erken tanısındaki klinik faydaları araştırıldı.

Bulgular: Sekiz yüz hastanın 159'una (% 19,8) GDM tanısı konuldu. GDM-Pozitif grup, GDM-Negatif gruba göre daha yüksek yaş, gravida, parite, VKİ ve ilk-trimester serum AKŞ düzeylerinin yanı sıra daha düşük serum PAPP-A MoM düzeylerine sahipti (P <0.05). Serum TSH ve f-βhCG, NT, AFP, uE3, ßhCG ve İnhibin-A MoM düzeyleri açısından gruplar arasında anlamlı fark yoktu. Lojistik regresyon analizinde, artan yaş (P=0.02, CI=1.007-1.096, OR=1.050), VKİ (P<0.01, CI=1.452-3.213, OR=1.107) ve ilk-trimester serum AKŞ düzeyleri GDM ile ilişkili bağımsız değişkenler olarak tespit edildi.

Sonuç: Birinci ve ikinci trimester antenatal tarama testlerinin GDM riskini öngörmede kullanılması anlamlı görünmemektedir. Bu testlerin Türk toplumunda GDM'nin erken tanısında kullanılabilirliğinin belirlenmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, antenatal tarama, risk değerlendirmesi

Cite as: Sarıoglu GB, Tas EE. Prediction of gestational diabetes mellitus risk in early pregnancy using antenatal screening biomarkers. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(3):255–260.

Geliş/Received: 27.07.2024 • **Kabul/Accepted:** 23.08.2024

Sorumlu Yazar/Corresponding Author: Emre Erdem TAS, Mehmet Akif Eroy Mahallesi Yesilay Caddesi 5A/121 Yenimahalle, Ankara/Turkey
E-mail: doctortas83@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as a glucose intolerance that first occurs or is diagnosed during pregnancy. GDM is a common complication of pregnancy associated with maternal and neonatal morbidities, including preeclampsia, polyhydramnios, fetal macrosomia, sudden infant death, and the risk of developing type 2 diabetes after pregnancy (1). The prevalence of GDM gradually increases with the average maternal age during pregnancy and rates of obesity (2).

GDM was diagnosed based on the results of a one-step 75 g OGTT or two-step 50 g screening and a 100 g OGTT performed at 24-28 weeks of gestation (3-5). Identification of pregnant women at a high risk of GDM in early pregnancy is important to facilitate preventive intervention, improve clinical outcomes, reduce maternal and fetal exposure to metabolic alterations, and improve antenatal care. Early diagnosis and treatment of GDM can significantly reduce maternal and fetal complications. The diagnosis of GDM after 24 weeks of gestation may lead to prolonged exposure to intrauterine hyperglycemia and macrosomia(6).

The first trimester dual screening test uses serum biochemical parameters such as free beta human chorionic gonadotropin (f-ßhCG), pregnancy-associated plasma protein-A (PAPP-A), and fetal nuchal translucency (NT). The second trimester quadruple screening test uses the serum biochemical parameters alpha fetoprotein (AFP), unconjugated estriol (uE3), ßhCG and Inhibin-A. These markers, which have been used to screen for genetic abnormalities in recent years, have also been reported to predict pregnancy complications such as preeclampsia, GDM, and intrauterine growth restriction (7-10).

In recent years, the number of studies on the diagnosis of GDM during early pregnancy has increased. Some studies have been published that explored the relationship between antenatal screening tests and GDM (11-14). However, there is still a lack of sufficient studies on this topic, and no definitive conclusions have been reached. This study aimed to investigate the relationship between GDM and the demographic, clinical, and dual or quadruple antenatal screening test characteristics of pregnant women.

MATERIAL AND METHODS

This retrospective cohort study was conducted at the Gynecology and Obstetrics Department of the Ankara Education and Research Hospital. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the same institute (date: 27/08/2020, Approval no. -20 406). Written informed consent was obtained from all participants prior to their participation in the study.

This study investigated 1184 pregnant women who underwent a one-step 75-gr Oral Glucose Tolerance Test (OGTT) and antenatal screening tests (double and quadruple screening tests) at obstetric polyclinics between January 2017 and June 2020. Patient age, gravidity and parity, body mass index (BMI) (kg/m^2), smoking status, first-trimester serum fasting blood glucose (FBG) and thyroid-stimulating hormone (TSH) levels, double and quadruple antenatal screening test MoM values, and 75-gr OGTT levels were extracted from electronic medical reports. We also recorded whether the patients had an additional medical condition or had used assisted reproductive techniques.

Pregnant women with multiple pregnancies, pregnancies conceived using assisted reproductive techniques, pregestational diabetes or diabetes diagnosed in early pregnancy, any chronic disease, and smokers were excluded from the study. In the remaining cases, GDM was diagnosed according to the criteria of the International Association of Diabetes and Pregnancy Study Group (IADPSG) (at least one elevated value in a one-step 75-g OGTT performed between 24- and 28-weeks' gestation)(4).

After the patients were divided into positive and negative GDM screening test groups, the groups (GDM-Positive vs. GDM-Negative) were compared in terms of the examined parameters. Once the parameters significantly associated with GDM were determined, their clinical utility in the early diagnosis of GDM was investigated.

Statistical Analysis

Data are expressed as mean ± standard deviation. The groups (GDM-Positive and GDM-Negative) were compared using independent-sample t-tests. Variables with $p<0.05$ were included in the binary logistic regression analysis, and the influence of each factor on the early diagnosis of GDM was evaluated. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 1186 patients, 386 (32.5%) were excluded from the study due to chronic comorbidities, multiple pregnancies, missing data, or smoking. Of the remaining 800 patients, 159 (19.8%) were diagnosed with GDM. A flow diagram of the participants recruited for the study is presented in Figure 1.

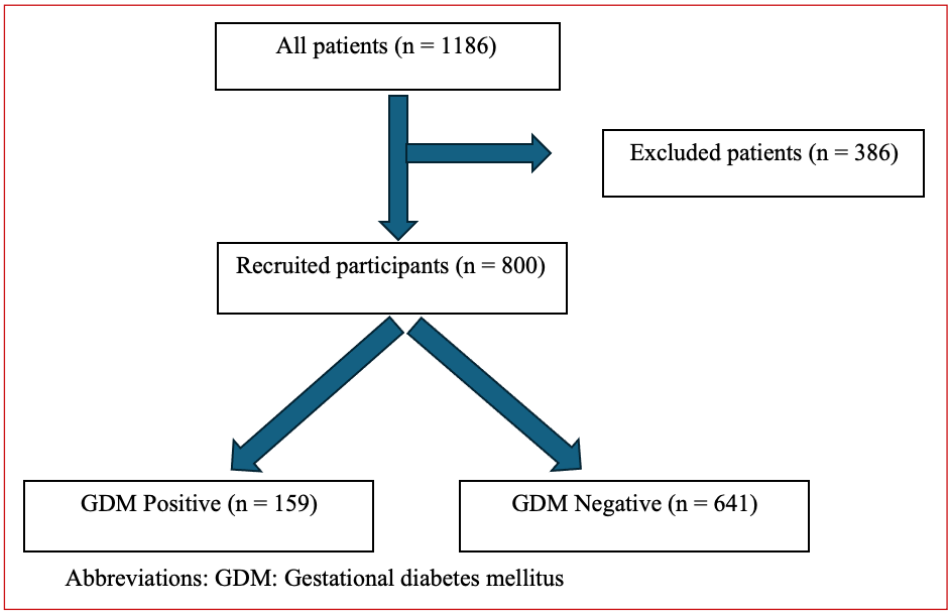

Figure 1. Flow diagram of the study recruitment process.

Table 1. The demographic and clinical characteristics of all patients and GDM-Positive and GDM-Negative groups

Characteristics, mean ± SD	All cases (n = 800)	GDM-Positive (n = 159)	GDM-Negative (n = 641)	P Value
Age (years)	27.0 ± 5.5	28.7 ± 5.4	26.6 ± 5.4	<0.01
Gravidity	2.4 ± 1.2	2.6 ±1.2	2.3 ±1.1	0.01
Parity	1.1 ± 0.9	1.3 ± 0.9	1.0 ± 0.9	<0.01
BMI (kg/m²)	25.2 ± 6.2	27.3 ± 4.8	24.7 ± 4.3	<0.01
First-trimester FBG (mg/dl)	87.3 ± 11.5	90.4 ± 3.1	85.9 ± 10.9	<0.01
TSH (mU/ml)	1.8 ± 2.0	1.8 ± 1.6	1.8 ± 2.1	0.78
PAPP-A MoM	1.1 ± 0.6	1.0 ± 0.6	1.1 ± 0.5	<0.01
f-βhCG MoM	1.1 ± 0.5	1.0 ± 0.6	1.1 ± 0.5	0.34
NT MoM	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.75
AFP MoM	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.29
uE3 MoM	1.1 ±0.1	1.1 ±0.3	1.1 ±0.3	0.59
ßhCG MoM	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.5	0.64
Inhibin-A MoM	1.1 ± 0.5	1.0 ± 0.4	1.1 ± 0.5	0.14

AFP: Alpha Feto Protein, BMI: Body mass index, FBG: Fasting blood glucose, f-ßhCG: Free Beta Human Chorionic Gonadotropin, GDM: Gestational Diabetes Mellitus, MoM: Multiples of Median, NT: Nuchal Translucency, TSH: Thyroid Stimulating Hormone, PAPP-A: Pregnancy Associated Plasma Protein-A, uE3: Unconjugated Estriol, ßhCG: Beta Human Chorionic Gonadotropin.

The demographic and clinical characteristics of all patients and groups (GDM-Positive and GDM-Negative) included in this study are presented in Table 1. When the groups were compared, age, gravidity, parity, BMI, and first-trimester serum FBG levels were significantly higher, whereas serum PAPP-A MoM levels were significantly lower in the GDM-Positive group than in the GDM-Negative group (P <0.05) (Table 1). There were no significant differences between the groups based on serum TSH and f-βhCG, NT, AFP, uE3, ßhCG, and Inhibin-A MoM levels (Table 1).

Binary logistic regression analysis revealed that among the variables that differed significantly between the GDM-Positive

Table 2. Binary logistic regression analysis of risk factors associated with GDM-positive group

	P value	95% CI	RR
Age (years)	**0.02**	1.007 – 1.096	1.050
Gravidity	0.55	0.669 – 1.239	-
Parity	0.40	0.794 – 1.769	-
First-trimester FBG (mg/dl) **BMI (kg/m²)**	**<0.01** **<0.01**	1.060 – 1.157 1.452 – 3.213	1.042 1.107
PAPP-A MoM	0.68	0.660 – 1.313	

BMI: Body mass index; FBG: Fasting blood glucose; GDM, gestational diabetes mellitus; MoM, multiples of median; PAPP-A, pregnancy-associated plasma protein-A.

and GDM-Negative groups, increased age, first trimester serum FBG levels, and BMI were independently associated with GDM (Table 2).

DISCUSSION

The incidence of GDM varies according to the population and diagnostic criteria. Studies using the traditional Carpenter and Coustan criteria have shown a prevalence of between 2% and 38% in different populations (15). However, the global prevalence of GDM is estimated to be approximately 17% according to the IADPSG (16). In a recent review of the results of studies conducted in different regions to determine the prevalence of GDM in Turkey, the prevalence of GDM was found to be 20% when the IADPSG criteria were used (17). In this study, the prevalence of GDM was 19.8%, which is close to the general average in Turkey.

Increased maternal age is also a risk factor for GDM. The First and Second Trimester Evaluation of Risk trial showed a continuous positive association between advancing maternal age and the risk of adverse pregnancy outcomes, including GDM (18). In a review and systematic meta-analysis of over 120 million participants, Li et al. showed that GDM risk exhibited a linear relationship with maternal age (19). Similarly, in the present study the mean of maternal age significantly higher in GDM-Positive group than in the GDM-Negative group (28.7 years vs 27.0 years, p<0.01). Additionally, our study revealed that increased maternal age was an independent risk factor for GDM (P=0.02, CI=1.007-1.096, OR=1.050).

Our research demonstrated that gravidity and parity were significantly higher in the GDM-Positive group than in the GDM-Negative group (P <0.05). However, high gravidity or high parity alone did not serve as independent risk factors for GDM, as their respective P-values were 0.55 and 0.40. We posit that this finding is related to increasing age and BMI in the GDM-Positive group. Our study aligns with the findings of Boyko et al. and Al-Rowaily et al., who showed that, although GDM was more prevalent in parous women, the significant difference disappeared when the groups were equalized with respect to age and BMI (20, 21).

Several research efforts in the United States and other countries have shown an increased likelihood of developing GDM in overweight or obese women compared with those who are lean or of normal weight (3-5, 17, 22). In a recent meta-analysis, Chu et al. estimated that the risk of GDM is approximately two, four, and eight times higher among overweight, obese, and severely obese women, respectively, than among normal-weight pregnant women (22). Similarly, Karacam et al. reported in their meta-analysis that being overweight was a risk factor for GDM development in the Turkish population(17). In the present study, the mean BMI was significantly higher in GDM-Positive group than in GDM-Negative group (27.1 years vs 24.7 years, P<0.01), and increased BMI was an independent risk factor for GDM (P<0.01, CI=1.452-3.213, OR=1.107).

GDM and thyroid dysfunction are two of the most common endocrine disorders that occur during pregnancy. Some previous reports showed a higher prevalence of thyroid dysfunction among women with GDM than among controls, whereas other studies did not find any association (23). In the present study, we did not identify any significant differences in serum TSH values between the GDM Positive and-negative groups (p>0.05). On the other hand, in a retrospective study of more than 40.000 pregnant women,

Tong et al. showed a positive linear relationship between first-trimester FBG levels and GDM (24). Similarly, in the present study, the mean first-trimester FBG levels were significantly higher in the GDM Positive group than in the GDM Negative group (90.4 mg/dl vs 85.9 mg/dl, p<0.01). Additionally, our study revealed that the first-trimester FBG level was an independent risk factor for GDM (p<0.01, CI=1.060-1.157, OR=1.042).

In recent years, the usefulness of antenatal screening tests used in the first and second trimesters for fetal aneuploidy in the early diagnosis of GDM has been investigated and exciting results have been obtained. However, there are also inconsistencies in the results of these studies. For example, in two different studies examining the association of dual screening parameters with GDM, Borna et al. found a significant association only between low PAPP-A levels and GDM, while Genc et al. found a significant association only between low f-ßhCG and GDM (11, 12). To the best of our knowledge, no study has reported a significant association between NT and GDM. In this study, serum PAPP-A levels were significantly lower in the GDM Positive group than in the GDM Negative group (P <0.05). Our results were consistent with those reported by Borno et al (11). However, we did not identify low serum PAPP-A level as an independent risk factor for GDM (P=0.68). On the other hand, there are inconsistencies in the few studies that have evaluated the association between quadruplet screening test parameters and GDM. In a previous study, Yue et al. reported that increased serum hCG levels were associated with GDM; however, Snyder et al. reported that increased serum uE3 and inhibin-A levels were related with GDM (13, 14). In contrast to those studies, we did not demonstrate significant differences between the GDM Positive and GDM Negative groups based on serum AFP, uE3, ßhCG, and inhibin-A levels (P>0.05).

In conclusion, this study showed that advanced maternal age, increased BMI, and high first-trimester FBG levels are independent risk factors for GDM. However, unlike previous studies, we did not observe a significant relationship between antenatal screening tests and GDM. Further studies are needed to determine the usability of these tests for early diagnosis of GDM in the Turkish population.

Author Contributions

EET and GBS contributed to study conception and design. Data collection, analysis, interpretation, and drafting of the manuscript were performed by EET and GBS.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev. 2022;43(5):763-93.
2. Zehravi M, Maqbool M, Ara I. Correlation between obesity, gestational diabetes mellitus, and pregnancy outcomes: an overview. Int J Adolesc Med Health. 2021;33(6):339-45.
3. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014;103(3):341-63.
4. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
5. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018;131(2):e49-e64.
6. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. Eur J Obstet Gynecol Reprod Biol. 2003;109(1):41-4.
7. Caliskan R, Atis A, Aydin Y, Acar D, Kiyak H, Topbas F. PAPP-A concentrations change in patients with gestational diabetes. J Obstet Gynaecol. 2020;40(2):190-4.
8. Yanachkova V, Staynova R, Stankova T, Kamenov Z. Placental Growth Factor and Pregnancy-Associated Plasma Protein-A as Potential Early Predictors of Gestational Diabetes Mellitus. Medicina (Kaunas). 2023;59(2).
9. Huang J, Chu X, Chen Y. Correlation and diagnostic value of maternal serum alpha-fetoprotein level, predelivery age and body mass with gestational diabetes mellitus. Gynecol Endocrinol. 2021;37(1):83-7.
10. Quintanilla Rodriguez BS, Mahdy H. Gestational Diabetes. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
11. Borna S, Ashrafzadeh M, Ghaemi M, Eshraghi N, Hivechi N, Hantoushzadeh S. Correlation between PAPP-A serum levels in the first trimester of pregnancy with the occurrence of gestational diabetes, a multicenter cohort study. BMC Pregnancy Childbirth. 2023;23(1):847.
12. Genc S, Ozer H, Emeklioglu CN, Cingillioglu B, Sahin O, Akturk E, et al. Relationship between extreme values of first trimester maternal pregnancy associated plasma Protein-A, free-β-human chorionic gonadotropin, nuchal translucency and adverse pregnancy outcomes. Taiwan J Obstet Gynecol. 2022;61(3):433-40.
13. Yue CY, Zhang CY, Ying CM. Serum markers in quadruple screening associated with adverse pregnancy outcomes: A case-control study in China. Clin Chim Acta. 2020;511:278-81.
14. Snyder BM, Baer RJ, Oltman SP, Robinson JG, Breheny PJ, Saftlas AF, et al. Early pregnancy prediction of gestational diabetes mellitus risk using prenatal screening biomarkers in nulliparous women. Diabetes Res Clin Pract. 2020;163:108139.
15. Bilous RW, Jacklin PB, Maresh MJ, Sacks DA. Resolving the Gestational Diabetes Diagnosis Conundrum: The Need for a Randomized Controlled Trial of Treatment. Diabetes Care. 2021;44(4):858-64.
16. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103(2):176-85.
17. Karaçam Z, Çelİk D. The prevalence and risk factors of gestational diabetes mellitus in Turkey: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2021;34(8):1331-41.
18. Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Impact of maternal age on obstetric outcome. Obstet Gynecol. 2005;105(5 Pt 1):983-90.
19. Li Y, Ren X, He L, Li J, Zhang S, Chen W. Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of over 120 million participants. Diabetes Res Clin Pract. 2020;162:108044.

20. Boyko EJ, Alderman BW, Keane EM, Baron AE. Effects of childbearing on glucose tolerance and NIDDM prevalence. Diabetes Care. 1990;13(8):848-54.

21. Al-Rowaily MA, Abolfotouh MA. Predictors of gestational diabetes mellitus in a high-parity community in Saudi Arabia. East Mediterr Health J. 2010;16(6):636-41.

22. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070-6.

23. Pinto S, Croce L, Carlier L, Cosson E, Rotondi M. Thyroid dysfunction during gestation and gestational diabetes mellitus: a complex relationship. J Endocrinol Invest. 2023;46(9):1737-59.

24. Tong JN, Wu LL, Chen YX, Guan XN, Tian FY, Zhang HF, et al. Fasting plasma glucose in the first trimester is related to gestational diabetes mellitus and adverse pregnancy outcomes. Endocrine. 2022;75(1):70-81.