*ORIGINAL ARTICLE*

**Retrospective Cohort Study**

# Utility of oral glucose tolerance test in predicting type 2 diabetes following gestational diabetes: Towards personalized care

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## Abstract

*BACKGROUND*

Women with gestational diabetes mellitus (GDM) are at a seven-fold higher risk of developing type 2 diabetes (T2D) within 7-10 years after childbirth, compared with those with normoglycemic pregnancy. Although raised fasting blood glucose (FBG) levels has been said to be the main significant predictor of postpartum progression to T2D, it is difficult to predict who among the women with GDM would develop T2D. Therefore, we conducted a cross-sectional retrospective study to examine the glycemic indices that can predict postnatal T2D in Emirati Arab women with a history of GDM.

*AIM*

To assess how oral glucose tolerance test (OGTT) can identify the distinct GDM pathophysiology and predict possible distinct postnatal T2D subtypes.

## METHODS

The glycemic status of a cohort of 4603 pregnant Emirati Arab women, who delivered in 2007 at both Latifa Women and Children Hospital and at Dubai Hospital, United Arab Emirates, was assessed retrospectively, using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Of the total, 1231 women were followed up and assessed in 2016. The FBG and/or the 2-h blood glucose (2hrBG) levels after a 75-g glucose load were measured to assess the prevalence of GDM and T2D, according to the IADPSG and American Diabetes Association (ADA) criteria, respectively. The receiver operating characteristic curve for the OGTT was plotted and sensitivity, specificity, and predictive values of FBG and 2hrBG for T2D were determined.

## RESULTS

Considering both FBG and 2hrBG levels, according to the IADPSG criteria, the prevalence of GDM in pregnant Emirati women in 2007 was 1057/4603 (23%), while the prevalence of pre-pregnancy T2D among them, based on ADA criteria, was 230/4603 (5%). In the subset of women ($n$ = 1231) followed up in 2016, the prevalence of GDM in 2007 was 362/1231 (29.6%), while the prevalence of pre-pregnancy T2D was 36/1231 (2.9%). Of the 362 pregnant women with GDM in 2007, 96/362 (26.5%) developed T2D; 142/362 (39.2%) developed impaired fasting glucose; 29/362 (8.0%) developed impaired glucose tolerance, and the remaining 95/362 (26.2%) had normal glycemia in 2016. The prevalence of T2D, based on ADA criteria, stemmed from the prevalence of 36/1231 (2.9%) in 2007 to 141/1231 (11.5%), in 2016. The positive predictive value (PPV) for FBG suggests that if a woman tested positive for GDM in 2007, the probability of developing T2D in 2016 was approximately 24%. The opposite was observed when 2hrBG was used for diagnosis. The PPV value for 2hrBG suggests that if a woman was positive for GDM in 2007 then the probability of developing T2D in 2016 was only 3%.

## CONCLUSION

FBG and 2hrBG could predict postpartum T2D, following antenatal GDM. However, each test reflects different pathophysiology and possible T2D subtype and could be matched with a relevant T2D prevention program.

**Key Words:** Type 2 diabetes; Type 2 diabetes subtypes; Oral glucose tolerance test; Diabetes; Gestational diabetes mellitus subtypes

**Core Tip:** The oral glucose tolerance test (OGTT) remains the gold standard for assessing the risk of postnatal diabetes in women with gestational diabetes mellitus (GDM). Both the fasting blood glucose and 2-h blood glucose tests could predict postpartum abnormal glycemic status following antenatal GDM. However, each test reflects a different pathophysiology and possible subtype of type 2 diabetes (T2D). If fasting serum insulin measurements are added to an OGTT, additional data generated could distinguish T2D pathophysiology and possible subtypes. Information obtained could be used to match the T2D subtype with relevant prevention programs such as frequent follow-ups, lifestyle modifications, and new treatment protocols.

## INTRODUCTION

Hyperglycemia in pregnancy is observed in women who are already diagnosed with diabetes and in those whose first experience of hyperglycemia was during pregnancy. The latter is defined as gestational diabetes mellitus (GDM), a transitory condition in which women develop hyperglycemia during pregnancy that returns to normal after delivery. Women with GDM are at a seven-fold higher risk of developing type 2 diabetes (T2D) within 7-10 years after childbirth, compared with those with normoglycemic pregnancy[1-3]. However, it is unclear which of the women with GDM develop T2D.

Over the past 40 years, many studies have investigated the risk factors involved in the development of T2D after an index pregnancy with GDM[4-8]. The main identified factors included family history of diabetes, high body mass index (BMI), elevated fasting blood glucose (FBG) and elevated 2-h blood glucose (2hrBG) levels. Increased FBG levels has stood out as a significant predictor of postpartum progression to T2D [9-10]. Systematic reviews[11,12] summarized and quantified the contribution of risk factors to T2D development in women with a history of GDM.

GDM and T2D share similar genetic backgrounds and pathophysiological mechanisms regarding their development. Both conditions result from two major dysfunctions: a drop in peripheral sensitivity to insulin and failure of the β-cells of the pancreas to secrete insulin[13-14]. GDM is considered a variant of diabetes secondary to the release of placental hormones[15]. Therefore, it could be assumed that pregnancy reveals an existing predisposition for T2D.

T2D is increasingly being recognized as a highly heterogeneous disease, with varying clinical presentations, progressions, responses to treatment, and types of complications[16-21]. Both the FBG and 2hrBG tests have been used in the process of subtyping T2D and in explaining the heterogeneity of the disease. In a non-pregnant adult, the impaired uptake of glucose under fasting conditions, as detected by the FBG test, is reflective of hepatic insulin resistance with normal muscle insulin sensitivity accompanied by a decrease in early-phase insulin secretion. In contrast, the impaired tolerance for glucose, as detected by the 2hrBG test, indicates peripheral muscle insulin resistance, with defects in both early and late insulin secretions[22-28]. Therefore, FBG and 2hrBG tests seem to predict pathophysiology trajectories for T2D in non-pregnant adults and has, therefore, been used in the subtyping of the disease [16-21].

The FBG and 2hrBG tests have also been used to explain the heterogeneity of GDM. Several studies[29-32] have suggested that GDM could be subtyped into three groups: (1) the GDM-sensitivity group with predominant peripheral resistance to the action of insulin, exhibiting high BMI and elevated levels of FBG and serum leptin; (2) the GDM-secretion group with defective insulin secretion and low BMI values, similar to those in the normal glucose tolerance (NGT) group; and (3) the GDM-mixed group, characterized by both insulin sensitivity and secretion defects. Women in both the GDM-sensitivity and GDM-mixed groups have elevated FBG levels, compared with those in the NGT group. The OGTT remains the gold standard (GS) for the diagnosis of adult T2D[33] and for screening GDM[5]. The two main parameters of the OGTT, the FBG and 2hrBG tests, indicative of different pathophysiologies of the disease, are being consistently used in the attempts to subtype both adult T2D and GDM.

The Dubai Health Authority (DHA) has adopted a protocol for antenatal care based on the universal screening for hyperglycemia, using an OGTT at 24-28 gestational weeks. Although raised FBG levels has been said to be the main significant predictor of postpartum progression to T2D, it is difficult to predict who among the women with GDM would develop T2D. Therefore, in this retrospective cohort study, we examined the glycemic indices that can predict postnatal T2D in Emirati Arab women with a history of GDM. Data were extracted from routine hospital investigations of antenatal and postnatal care of women who delivered in 2007 in Latifa Women and Children Hospital and in Dubai Hospital, and were successfully followed-up in 2016.

## MATERIALS AND METHODS

### *Patients*

The present study was conducted in 2 hospitals: The Latifa Women and Children Hospital and Dubai Hospital; the 2 main public hospitals of the DHA, United Arab Emirates. The Latifa Women and Children Hospital is a 400-bed tertiary and referral hospital for obstetrics and gynecology and children care. Dubai Hospital is a 625-bed

center for referral of all medical and surgical specialties including obstetric services. Both hospitals share the same electronic health information system (HIS) called Salama.

Routine clinical and laboratory data for 4603 Emirati women, who delivered at the Latifa Women and Children Hospital ($n$ = 3121) and Dubai Hospital ($n$ = 1482) between January 1 and December 31, 2007, were collected from the "Salama" HIS. Of those women, 1231 (27%) were successfully followed up in 2016, and their data were compared with that of 2007. All 1231 women were included in the analysis. Therefore, no sample size or power analysis was performed.

### Methods

Blood glucose was enzymatically assayed in the laboratories at the Latifa Women and Children Hospital and Dubai Hospital, using hexokinase as reference on the Cobas 6000 Analyzer (Roche Diagnostics, Basel, Switzerland). The measuring range of this method is 0.11-41.6 mmol/L (2-750 mg/dL). The coefficients of variation of the method are 0.7% and 1.2% for low and high blood glucose levels, respectively.

The routine protocol for antenatal care at the Latifa Women and Children Hospital and Dubai Hospital included universal screening for hyperglycemia using an OGTT at 24-28 gestational weeks. The FBG level and/or the 2hrBG level after a 75-g glucose load were measured to assess the prevalence of GDM and T2D, according to the IADPSG[5] and the ADA[8], respectively. GDM is defined as an FBG level of 5.1-6.9 mmol/L (92-125 mg/dL), and/or a 2hrBG level of 8.5-11.0 mmol/L (153-199 mg/dL) on a 2-h 75-g OGTT. DM is defined as an FBG level ≥ 7.0 mmol/L (126 mg/dL) and/or a 2hrBG of ≥ 11.1 mmol/L (200 mg/dL).

The ADA criteria for the diagnosis of diabetes in non-pregnant adults[8] has been adopted by the DHA and employed in our analysis of oral glucose tolerance testing. The FBG level and/or 2hrBG after a 75-g glucose load were measured to assess the prevalence of T2D. Diabetes was defined by a level of FBG ≥ 7.0 mmol/L (126 mg/dL) or a 2hrBG level ≥ 11.1 mmol/L (200 mg/dL). Impaired fasting blood glucose (IFG) was defined by a level of 5.6-6.9 mmol/L (100-125 mg/dL), while impaired glucose tolerance (IGT) was defined by a 2hrBG level of 7.8-11.0 mmol/L (140-199 mg/dL).

The glycemic status of the cohort of women ($n$ = 1231) who were previously tested in 2007 was assessed again in 2016. Of those, 872 underwent FBG test only, 118 postprandial 2hrBG test only, while the remaining 241 had a complete OGTT.

The routine glycemic status of both the 4603 Emirati women in 2007 and the 1231 women who were followed up in 2016, were obtained from the Salama HIS. The women suspected of diabetes were confirmed and followed-up in either Hospital. The prevalence of T2D in the cohort of Emirati women tested in 2007 and the incidence of T2D during the 9-year period (2007-2016) were numerically calculated.

### Data analysis

Data were analyzed using SPSS software version 23 (IBM, Chicago, IL, United States). All continuous data were described as mean ± SD, while the categorical data were described as number and percentage.

According to the IADPSG criteria, a woman will be considered to have GDM, at any time in her reproductive life, if her blood glucose is within the cut-off values for GDM and does not reach the cut-off values for diabetes. The prevalence of GDM in 2007 was calculated as percentage of women with OGTT blood glucose levels within the cut-off values, stipulated by the IADPSG criteria (m), divided by the total number of women in the specified cohort (N): (m/N) ∗ 100. The incidence of diabetes in 2016 was calculated as the annual average of the difference over a 9-year period. Results were expressed as incidence rate and incidence density rate.

### Specificity and sensitivity of FBG and 2hrBG in predicting T2D

The open-source R-4.02 statistical software was used to plot the receiver operating characteristic (ROC) curve for the OGTT. The women were categorized as having GDM or normal glycemia based on their FBG and 2hrBG levels in 2007. The diagnosis of T2D in 2016 was considered the GS, using HbA1c levels. The diagnosis of T2D was confirmed by correlation of FBG and 2hrBG values with HbA1c levels (Pearson correlation at 0.798; $P$ ≤ 0.01). To find the best cut off values for the 2007 FBG level, the actual values were plotted against the GS results (T2D or normal). At each cut off value for the 2007 FBG level, the sensitivity and specificity were calculated by forming a 2 by 2 table with the GS results[34-36].

The best cut off values for FBG for predicting T2D from GDM were calculated using the Youden Index: [(sensitivity + specificity) - 1]. However, on testing the 2hrBG level

in 2016, only five women were classified as having T2D. Therefore, performing an analysis to find the best cut off value for 2hrBG was not feasible.

### Ethical considerations

This study was part of a project exploring hyperglycemia in pregnancy, funded by Al Jalila Foundation, Dubai, United Arab Emirates, under Grant No. AJF2015, dated November 8, 2015. Ethical approval was granted by the Dubai Scientific Research Ethics Committee of the DHA, with Reference No. DSREC: 12/2015_05; dated November 29, 2015. Data were anonymously collected for each participant in the study.

## RESULTS

### Demographics of Emirati women successfully followed up in 2016

Table 1 summarizes the age, BMI, parity, and outcomes of pregnancy in 1231 Emirati women, who delivered at Latifa Women and Children Hospital and Dubai Hospital in 2007 and were successfully followed up in 2016.

### Prevalence of GDM and T2D in 2007

Combining the FBG and 2hrBG IADPSG criteria, the prevalence of GDM in pregnant Emirati women in 2007 was 1057/4603 (23%), while that of pre-pregnancy T2D, based on ADA criteria, was 230/4603 (5%). Among the subset of women (*n* = 1231) followed up in 2016 (Table 2), the prevalence of GDM in 2007 was 362/1231 (29.4%), while that of pre-pregnancy T2D was 36/1231 (2.9%). The proportion of women diagnosed with GDM based on a raised FBG level (267) was 1.8 times higher than that of those diagnosed based on a raised 2hrBG level (147).

### Incidence of T2D in 2016

The glycemic status in 2016 of the same cohort of women (*n* = 1231), who were previously tested in 2007, is displayed in Table 3. Of those, 872 underwent FBG test only, 118 postprandial 2hrBG test only, while the remaining 241 underwent a complete OGTT. Based on the ADA criteria, the overall number of women who developed T2D increased from 36 (2.9%) in 2007 to 141 (11.5%) in 2016, a four-fold increase (Tables 2 and 3). The incidence of T2D over a 9-year period was estimated as follows: (141 – 36 = 105)/9 = 11.7 per 1000 Emirati women per year. All the women tested in the initial observation period in 2007 were also tested during the follow-up period in 2016. Therefore, the incidence density of T2D was the same as the incidence rate.

### Conversion of GDM to T2D

To measure the conversion rate of GDM to T2D, the IADPSG glycemic indices of the cohort of Emirati women in 2007 (*n* = 1231) were cross tabulated against the ADA glycemic indices of the same cohort in 2016 (Table 4). Based on the isolated FBG, out of the 267 pregnant women with GDM in 2007, 69 (26 %) developed T2D, 89 (33%) developed IFG, 9 (3%) developed IGT, and the remaining 100 (38%) had normal glycemia in 2016.

Regarding isolated 2hrBG, out of the 147 pregnant women with GDM in 2007, 27 (18%) developed T2D, 53 (36%) developed IFG, 20 (14%) developed IGT, and the remaining 47 (32%) had normal glycemia in 2016. Based on associated FBG and 2hrBG, out of the 362 pregnant women with GDM in 2007, 96 (27%) developed T2D, 142 (39%) developed IFG, 29 (8.0%) developed IGT, and the remaining 95 (26%) had normal glycemia in 2016.

The conversion rate of GDM to IFG (33%-39%), was much higher than that of GDM to IGT (3%-14%). The prevalence of T2D, based on ADA criteria increased from 36/1231 (2.9%) in 2007 to 141/1231 (11.5%), in 2016. Women with raised FBG levels had a higher risk of developing T2D, compared with those with raised postprandial 2hrBG levels.

The sensitivity and specificity of FBG and 2hrBG tests in predicting T2D following GDM in Emirati women are shown in Table 5. The sensitivity of FBG was 82.3% (95%CI: 72.1, 90.0) while specificity was 55.1% (95%CI: 0.50, 0.60). The PPV for FBG of 24.3% suggests that, if a woman was positive for GDM in 2007, the probability of developing T2D in 2016 was about 24%. The negative predictive value (NPV) for FBG implied that, if a woman was negative for GDM in 2007, the probability of maintaining normal FBG levels was about 95%.

**Table 1 Demographic characteristics of Emirati women who delivered in 2007 in Latifa Women and Children Hospital and Dubai Hospital, and were successfully followed up in 2016[1]**

|  | mean ± SD |
|---|---|
| Number (*n*) | 1231 |
| Age (yr) | 38.7 ± 6.1 |
| BMI (kg/m$^2$) | 31.1 ± 6.7 |
| Parity (*n*) | 5.74 ± 3.3 |
| Live born (*n*) | 4.53 ± 3.0 |
| Still birth (*n*) | 0.1 ± 0.3 |
| Miscarriage (*n*) | 1.1 ± 1.7 |

[1]Data were obtained in 2016.
BMI: Body mass index.

**Table 2 Results of oral glucose tolerance test of 1231 Emirati pregnant women performed during their 24-28 wk of pregnancy in 2007, *n* (%)**

| Positive Diagnostic criteria[1] | Normal | GDM | T2D |
|---|---|---|---|
| Isolated FBG | 995 (80.8) | 215 (17.5) | 21 (1.7) |
| Isolated 2hrBG | 1121 (91.0) | 95 (7.7) | 15 (1.2) |
| Associated FBG and 2hrGB | 1179 (95.8) | 52 (4.2) | 0 (0) |
| Total | 833 (67.7) | 362 (29.4) | 36 (2.9) |

[1]International Association of Diabetes and Pregnancy Study Groups (IADPSG)[5] criteria.
OGTT: Oral glucose tolerance test; GDM: Gestational diabetes mellitus; T2D: Type 2 diabetes; FBG: Fasting blood glucose; 2hrBG: 2-h blood glucose.

**Table 3 Glycemic status of 1231 Emirati pregnant women, who were tested previously in 2007, and underwent post-natal glycemic tests in 2016**

| Diagnostic criteria[1] | Total number tested | Normal | Impaired FBG | IGT | Impaired FBG and IGT | T2D |
|---|---|---|---|---|---|---|
| FBG | 872 | 542 | 203 | - | - | 127 |
| Post-prandial 2hrBG | 118 | 86 | - | 28 | - | 4 |
| OGTT | 241 | 146 | 23 | 52 | 10 | 10 |
| Total | 1231 | 774 | 226 | 80 | 10 | 141 |

[1]American Diabetes Association criteria for diagnosis of diabetes mellitus[8].
FBG: Fasting blood glucose; IGT: Impaired glucose tolerance; T2D: Type 2 diabetes; 2hrBG: 2-h blood glucose; OGTT: Oral glucose tolerance test.

The opposite is being observed in the predictability of T2D in 2016 using the 2hrBG in the diagnosis of GDM in 2007. The sensitivity of the 2hrBG test was 20.0% (95%CI: 0.05, 0.716), while the specificity was 88.3% (95%CI: 0.845, 0.92). The PPV value suggests that if a woman was positive for GDM in 2007, the probability of developing T2D in 2016 was about 3%. The NPV implied that if a woman was negative for GDM in 2007, the probability of maintaining normal 2hrBG levels was about 98%.

The sensitivities and specificities of various cut-off values for FBG in 2007 were estimated against the test results in 2016 (GS: T2D and normal). Using the Youden Index, a cut off value of FBG ≥ 103 mg/dL in 2007, above which T2D was diagnosed in 2016, was identified. This cut off value provided a sensitivity and specificity of 76.9% and 68.1% respectively. The area under the ROC Curve was 77.2% ($P < 0.001$). Thus, the FBG level ≥ 103 mg/dL at 2007 significantly predicted the T2D status in 2016. The 2hrBG levels could not be tested due to the small number who converted to T2D.

**Table 4 Cross-tabulation of the glycemic status of Emirati women (*n* = 1231) who delivered in 2007, against their glycemic status in 2016, *n* (%)**

| IADPSG diagnostic criteria for GDM (2007) | ADA diagnostic criteria (2016) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fasting | | | | 2 h | | | |
| | Total | Normal | IFG | T2D | Total | Normal | IGT | T2D |
| Fasting | | | | | | | | |
| Normal | 262 (100) | 205 (78) | 43 (16) | 14 (5) | 89 (100) | 54 (61) | 30 (34) | 5 (5) |
| GDM | 267 (100) | 113 (42) | 89 (33) | 65 (25) | 44 (100) | 31 (70) | 9 (21) | 4 (9) |
| T2D | 26 (100) | 2 (8) | 3 (11) | 21 (81) | 2 (100) | 1 (50) | 1 (50) | 0 (0) |
| Total | 555 (100) | 320 (58) | 135 (24) | 100 (18) | 135 (18) | 86 (64) | 40 (29) | 9 (7) |
| 2Hr | | | | | | | | |
| Normal | 670 (100) | 495 (74) | 138 (21) | 37 (5) | 252 (100) | 197 (78) | 51 (20) | 4 (2) |
| GDM | 147 (100) | 68 (46) | 53 (36) | 26 (18) | 34 (100) | 13 (38) | 20 (59) | 1 (3) |
| T2D | 26 (100) | 7 (27) | 5 (19) | 14 (54) | 4 (100) | 1 (25) | 2 (50) | 1 (25) |
| Total | 843 (100) | 843 (68) | 196 (23) | 77 (9) | 290 (100) | 211 (73) | 73 (25) | 6 (2) |

GDM: Gestational diabetes mellitus; T2D: Type 2 diabetes; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; FBG: Fasting blood glucose; 2hrBG: 2-h blood glucose.

**Table 5 Sensitivity and specificity of fasting blood glucose and 2-h blood glucose in predicting type 2 diabetes following gestational diabetes mellitus in Emirati women[1]**

| IADPSG diagnostic criteria for GDM (2007) | ADA diagnostic criteria for T2D (2016) | | | |
|---|---|---|---|---|
| | FBG | | 2hrBG | |
| | T2D (*n*) | Normal (*n*) | T2D (*n*) | Normal (*n*) |
| GDM | 65 | 202 | 1 | 33 |
| Normal | 14 | 248 | 4 | 248 |
| Point estimates and 95%CIs | | | | |
| True prevalence | 0.149 (0.12, 0.183) | | 0.017 (0.006, 0.04) | |
| Sensitivity | 0.823 (0.721, 0.9) | | 0.200 (0.005 0.716) | |
| Specificity | 0.551 (0.504, 0.598) | | 0.883 (0.839, 0.918) | |
| Positive predictive value | 0.243 (0.193, 0.299) | | 0.029 (0.001, 0.153) | |
| Negative predictive value | 0.947 (0.912, 0.97) | | 0.984 (0.96, 0.996) | |
| Positive likelihood ratio | 1.833 (1.586, 2.118) | | 1.703 (0.287, 10.12) | |
| Negative likelihood ratio | 0.322 (0.198, 0.521) | | 0.906 (0.584, 1.408) | |
| Odds ratio | 5.7 (3.108, 10.455) | | 1.879 (0.204, 17.32) | |

[1]The R 4.02 statistical software was used to plot the receiver operating characteristic curve.

GDM: Gestational diabetes mellitus; T2D: Type 2 diabetes; FBG: Fasting blood glucose; 2hrBG: 2-h blood glucose.

## DISCUSSION

Most studies that assessed the risk of developing T2D following a history of GDM were conducted in prospective clinical trials[1-7]. In contrast, our cross-sectional retrospective study analyzed the clinical and laboratory data of a cohort of Emirati Arab women, obtained from the routine clinical practice in a tertiary obstetrics set-up. The data were intended for clinical service; however, it proved to be useful for determining the risk of T2D in women with a history of GDM nine years earlier. The results suggested that both raised FBG and 2hrBG levels are sensitive glycemic

indicators of transition to prediabetes and T2D. Out of the 362 pregnant women with GDM in 2007, 27% developed T2D, 39% developed IFG, 8.0% developed IGT, and the remaining 26% had normal glycemia in 2016. The prevalence of T2D, based on the ADA criteria, increased from 2.9% in 2007 to 11.5%, in 2016. The conversion rate of GDM to T2D was higher in women with raised FBG levels (26%) than in women with raised 2hrBG levels (18%), indicating that the former group had a higher risk of developing T2D than the latter group. This was further supported by the OGTT ROC Curve indices. The PPV for FBG suggests that if a woman tested positive for GDM in 2007, the probability of developing T2D in 2016 was approximately 24%. The opposite is being observed in the predictability of T2D in 2016, using the 2hrBG. The PPV value suggests that, if a woman was positive for GDM in 2007, the probability of developing T2D in 2016 was only 3%. A similar trend of higher conversion rate of GDM to IFG was observed among women with raised FBG levels, compared with the rate of conversion of GDM to IGT among those with increased IGT. Our results agree with those of numerous previous studies referenced in several systematic reviews and meta-analyses[1-4,6-7,11-12].

The impaired uptake of glucose under fasting conditions, as detected by the FBG test, is reflective of hepatic insulin resistance with normal muscle insulin sensitivity accompanied by a decrease in the early-phase insulin secretion. In contrast, the impaired tolerance for glucose, as detected by the 2hrBG test, indicates peripheral muscle insulin resistance with defects in both early and late insulin secretion[22-28]. It is suggested that women with these two distinct metabolic states represent two distinct subtypes of GDM[29-32], depending on the defects in insulin sensitivity and/or secretion. A GDM-sensitivity group with predominant peripheral resistance to the action of insulin exhibited high BMI and elevated levels of FBG and serum leptin. Patients with defective insulin secretion, the GDM-secretion group, had low BMI values, similar to those in the NGT group. The third group is the GDM-mixed group, characterized by both insulin sensitivity and secretion defects. Women in both the GDM-sensitivity group and GDM-mixed group had elevated FBG levels compared with those in the NGT group. Earlier studies on the risk of T2D following GDM did not consider these proposed subtypes of GDM[1-3]. It is possible, therefore, that the GDM subgroup in our cohort of Emirati women, with raised FBG levels and higher conversion rate to T2D, is congruent with the GDM-sensitivity group characterized by peripheral insulin resistance; whereas, the GDM subgroup with raised 2hrBG levels reflected insulin secretion defects[29-32].

Subtyping of both adult non-pregnant with T2D[16-21] and GDM[29-32] patients represent serious attempts at resolving the heterogeneity of T2D, bringing the idea of personalized care closer, as pathophysiology is used to distinguish subtypes from each other. Different clinical management schemes are then tailored for each subtype. The use of the OGTT as a diagnostic tool has been discouraged over the past 20 years for various reasons[33]. However, insulin secretion and resistance could easily be deduced from assessing HOMA-B and HOMA-IR, if fasting serum insulin is measured during routine OGTT. The latter could then be instrumental in predicting T2D patho-physiology and possible subtypes.

A modified OGTT could become a powerful tool if extra parameters like fasting insulin and C-peptide, are measured simultaneously. It will help in identifying T2D subtypes and brings personalized patient care closer. Subtypes could then be matched with specific prevention programs like frequent follow-ups, lifestyle modifications, and new treatment protocols.

### *Limits of the study*

This study, being retrospective in design, is limited. Fasting insulin and other hormones levels were not measured during routine hospital investigations. We could not obtain the indices for both secretion and resistance to the action of insulin, such as HOMA-B and HOMA-IR. A detailed prospective study will be essential for examining the trajectory of the conversion of GDM to T2D and the role that a modified OGTT could play in the dissection of the pathogenesis of the disease.

## CONCLUSION

This cross-sectional retrospective cohort study, conducted among Emirati Arab women with GDM, revealed that raised antenatal FBG and 2hrBG levels could predict postpartum T2D; however, it suggested that each parameter may indicate a distinct T2D pathophysiology. Women with predominant peripheral resistance to the action of

insulin, who have raised FBG levels during pregnancy, were at a greater risk of developing T2D, compared with those with raised postprandial 2hrBG levels. It is suggested that, for the former group of women, postnatal management like frequent follow-ups, lifestyle modifications, and specific treatment protocols, should be applied to slow down the development of T2D and improve the quality of life for them and their newborns.

## ARTICLE HIGHLIGHTS

### Research background

Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy. It has short- and long-term maternal, fetal, and neonatal complications. Women with GDM are at a seven-fold higher risk of developing type 2 diabetes (T2D) within 7-10 years after childbirth, compared with those with normoglycemic pregnancy.

### Research motivation

There is emerging evidence that both GDM and T2D can be subtyped according to their pathophysiology. We attempted to examine the link between subtypes of GDM and the prediction of postnatal T2D.

### Research objectives

To assess the utility of oral glucose tolerance test (OGTT) in the identification of distinct GDM pathophysiology and in the prediction of possible distinct postnatal T2D subtypes.

### Research methods

The glycemic status of a cohort of 4603 pregnant Emirati Arab women, who delivered in 2007 in Dubai United Arab Emirates, was assessed retrospectively, using OGTT according to the International Association of Diabetes and Pregnancy Study Groups criteria. Of the total, 1231 women were followed up and assessed in 2016. The receiver operating characteristic curve for the OGTT was plotted and sensitivity, specificity, and predictive values of fasting blood glucose (FBG) and 2hrBG for T2D were estimated.

### Research results

The prevalence of GDM in pregnant Emirati women in 2007 was 1057/4603 (23%), while the prevalence of pre-pregnancy T2D based on ADA criteria, was 230/4603 (5%). In the subset of women ($n$ = 1231) followed up in 2016, the prevalence of GDM in 2007 was 362/1231 (29.6%), while the prevalence of pre-pregnancy T2D, was 36/1231 (2.9%). Of the 362 pregnant women with GDM in 2007, 96/362 (26.5%) developed T2D, 142/362 (39.2%) developed impaired fasting glucose, 29/362 (8.0%) developed impaired glucose tolerance, and the remaining 95/362 (26.2%) had normal glycemia in 2016. The prevalence of T2D, based on ADA criteria, stemmed from the prevalence of 36/1231 (2.9%) in 2007 to 141/1231 (11.5%), in 2016. The positive predictive value (PPV) for FBG suggests that, if a woman is positive for GDM in 2007, then the probability of developing T2D in 2016 was about 24%. The opposite is being observed in the predictability of T2D in 2016 using the 2hrBG in diagnosis of GDM in 2007. The PPV value suggests that if a woman was positive for GDM in 2007 then the probability of developing T2D in 2016 was only 3%.

### Research conclusions

The results of this study revealed that both raised antenatal FBG and 2hrBG levels could predict postpartum T2D; however, it suggested that each parameter may indicate a distinct T2D pathophysiology. Women with predominant peripheral resistance to the action of insulin, who have raised FBG levels during pregnancy, were at a greater risk of developing T2D, compared with those with raised postprandial 2hrBG levels.

### Research perspectives

Our findings suggested that, for women who at a greater risk of developing T2D, postnatal management like frequent follow-ups, lifestyle modifications, and specific treatment protocols, should be applied to slow down the development of T2D and improve the quality of life for them and their newborns.

## REFERENCES

1    **Kim C**, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002; **25**: 1862-1868 [PMID: 12351492 DOI: 10.2337/diacare.25.10.1862]

2    **Bellamy L**, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; **373**: 1773-1779 [PMID: 19465232 DOI: 10.1016/S0140-6736(09)60731-5]

3    **International Association of Diabetes in Pregnancy Study Group (IADPSG) Working Group on Outcome Definitions**, Feig DS, Corcoy R, Jensen DM, Kautzky-Willer A, Nolan CJ, Oats JJ, Sacks DA, Caimari F, McIntyre HD. Diabetes in pregnancy outcomes: a systematic review and proposed codification of definitions. *Diabetes Metab Res Rev* 2015; **31**: 680-690 [PMID: 25663190 DOI: 10.1002/dmrr.2640]

4    **Golden SH**, Bennett WL, Baptist-Roberts K, Wilson LM, Barone B, Gary TL, Bass E, Nicholson WK. Antepartum glucose tolerance test results as predictors of type 2 diabetes mellitus in women with a history of gestational diabetes mellitus: a systematic review. *Gend Med* 2009; **6** Suppl 1: 109-122 [PMID: 19318222 DOI: 10.1016/j.genm.2008.12.002]

5    **International Association of Diabetes and Pregnancy Study Groups Consensus Panel**, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33**: 676-682 [PMID: 20190296 DOI: 10.2337/dc09-1848]

6    **Rayanagoudar G**, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. *Diabetologia* 2016; **59**: 1403-1411 [PMID: 27073002 DOI: 10.1007/s00125-016-3927-2]

7    **Tobias DK**. Prediction and Prevention of Type 2 Diabetes in Women with a History of GDM. *Curr Diab Rep* 2018; **18**: 78 [PMID: 30117058 DOI: 10.1007/s11892-018-1063-8]

8    **American Diabetes Association**. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2020. Diabetes Care* 2020; **43**: S14-S31 [PMID: 31862745 DOI: 10.2337/dc20-S002]

9    **Cheung NW**, Helmink D. Gestational diabetes: the significance of persistent fasting hyperglycemia for the subsequent development of diabetes mellitus. *J Diabetes Complications* 2006; **20**: 21-25 [PMID: 16389163 DOI: 10.1016/j.jdiacomp.2005.05.001]

10   **Cosson E**, Carbillon L, Valensi P. High Fasting Plasma Glucose during Early Pregnancy: A Review about Early Gestational Diabetes Mellitus. *J Diabetes Res* 2017; **2017**: 8921712 [PMID: 29181414 DOI: 10.1155/2017/8921712]

11   **Buchanan TA**, Xiang AH. Gestational diabetes mellitus. *J Clin Invest* 2005; **115**: 485-491 [PMID: 15765129 DOI: 10.1172/JCI24531]

12   **Barbour LA**, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care* 2007; **30** Suppl 2: S112-S119 [PMID: 17596458 DOI: 10.2337/dc07-s202]

13   **Kramer CK**, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, Zinman B, Retnakaran R. Each degree of glucose intolerance in pregnancy predicts distinct trajectories of β-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum. *Diabetes Care* 2014; **37**: 3262-3269 [PMID: 25231898 DOI: 10.2337/dc14-1529]

14   **Tura A**, Grassi A, Winhofer Y, Guolo A, Pacini G, Mari A, Kautzky-Willer A. Progression to type 2 diabetes in women with former gestational diabetes: time trajectories of metabolic parameters. *PLoS One* 2012; **7**: e50419 [PMID: 23185618 DOI: 10.1371/journal.pone.0050419]

15   **Newbern D**, Freemark M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes* 2011; **18**: 409-416 [PMID: 21986512 DOI: 10.1097/MED.0b013e32834c800d]

16   **Ahlqvist E**, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; **6**: 361-369 [PMID: 29503172 DOI: 10.1016/S2213-8587(18)30051-2]

17   **Udler MS**, Kim J, von Grotthuss M, Bonàs-Guarch S, Cole JB, Chiou J; Christopher D. Anderson on

behalf of METASTROKE and the ISGC, Boehnke M, Laakso M, Atzmon G, Glaser B, Mercader JM, Gaulton K, Flannick J, Getz G, Florez JC. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS Med* 2018; **15**: e1002654 [PMID: 30240442 DOI: 10.1371/journal.pmed.1002654]

18    **Dennis JM**, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019; **7**: 442-451 [PMID: 31047901 DOI: 10.1016/S2213-8587(19)30087-7]

19    **Kahkoska AR**, Geybels MS, Klein KR, Kreiner FF, Marx N, Nauck MA, Pratley RE, Wolthers BO, Buse JB. Validation of distinct type 2 diabetes clusters and their association with diabetes complications in the DEVOTE, LEADER and SUSTAIN-6 cardiovascular outcomes trials. *Diabetes Obes Metab* 2020; **22**: 1537-1547 [PMID: 32314525 DOI: 10.1111/dom.14063]

20    **Ahlqvist E**, Prasad RB, Groop L. Subtypes of Type 2 Diabetes Determined From Clinical Parameters. *Diabetes* 2020; **69**: 2086-2093 [PMID: 32843567 DOI: 10.2337/dbi20-0001]

21    **Anjana RM**, Pradeepa R, Unnikrishnan R, Tiwaskar M, Aravind SR, Saboo B, Joshi SR, Mohan V. New and Unique Clusters of Type 2 Diabetes Identified in Indians. *J Assoc Physicians India* 2021; **69**: 58-61 [PMID: 33527813]

22    **Gerstein HC**. Fasting versus postload glucose levels: why the controversy? *Diabetes Care* 2001; **24**: 1855-1857 [PMID: 11679446 DOI: 10.2337/diacare.24.11.1855]

23    **Carnevale Schianca GP**, Rossi A, Sainaghi PP, Maduli E, Bartoli E. The significance of impaired fasting glucose versus impaired glucose tolerance: importance of insulin secretion and resistance. *Diabetes Care* 2003; **26**: 1333-1337 [PMID: 12716784 DOI: 10.2337/diacare.26.5.1333]

24    **Abdul-Ghani MA**, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006; **29**: 1130-1139 [PMID: 16644654 DOI: 10.2337/diacare.2951130]

25    **Nathan DM**, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; **30**: 753-759 [PMID: 17327355 DOI: 10.2337/dc07-9920]

26    **Faerch K**, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? *Diabetologia* 2009; **52**: 1714-1723 [PMID: 19590846 DOI: 10.1007/s00125-009-1443-3]

27    **Abdul-Ghani MA**, DeFronzo RA. Pathophysiology of prediabetes. *Curr Diab Rep* 2009; **9**: 193-199 [PMID: 19490820 DOI: 10.1007/s11892-009-0032-7]

28    **Hulman A**, Witte DR, Vistisen D, Balkau B, Dekker JM, Herder C, Hatunic M, Konrad T, Færch K, Manco M. Pathophysiological Characteristics Underlying Different Glucose Response Curves: A Latent Class Trajectory Analysis From the Prospective EGIR-RISC Study. *Diabetes Care* 2018; **41**: 1740-1748 [PMID: 29853473 DOI: 10.2337/dc18-0279]

29    **Powe CE**, Allard C, Battista MC, Doyon M, Bouchard L, Ecker JL, Perron P, Florez JC, Thadhani R, Hivert MF. Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. *Diabetes Care* 2016; **39**: 1052-1055 [PMID: 27208340 DOI: 10.2337/dc15-2672]

30    **Benhalima K**, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, Jacquemyn Y, Mekahli F, De Clippel K, Van Den Bruel A, Loccufier A, Laenen A, Minschart C, Devlieger R, Mathieu C. Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance. *Diabetologia* 2019; **62**: 2118-2128 [PMID: 31338546 DOI: 10.1007/s00125-019-4961-7]

31    **Ryan EA**, Savu A, Yeung RO, Moore LE, Bowker SL, Kaul P. Elevated fasting vs post-load glucose levels and pregnancy outcomes in gestational diabetes: a population-based study. *Diabet Med* 2020; **37**: 114-122 [PMID: 31705695 DOI: 10.1111/dme.14173]

32    **Powe CE**, Hivert MF, Udler MS. Defining Heterogeneity Among Women With Gestational Diabetes Mellitus. *Diabetes* 2020; **69**: 2064-2074 [PMID: 32843565 DOI: 10.2337/dbi20-0004]

33    **Jagannathan R**, Neves JS, Dorcely B, Chung ST, Tamura K, Rhee M, Bergman M. The Oral Glucose Tolerance Test: 100 Years Later. *Diabetes Metab Syndr Obes* 2020; **13**: 3787-3805 [PMID: 33116727 DOI: 10.2147/DMSO.S246062]

34    **Florkowski CM**. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. *Clin Biochem Rev* 2008; **29** Suppl 1: S83-S87 [PMID: 18852864]

35    **Power M**, Fell G, Wright M. Principles for high-quality, high-value testing. *Evid Based Med* 2013; **18**: 5-10 [PMID: 22740357 DOI: 10.1136/eb-2012-100645]

36    **Feizi A**, Meamar R, Eslamian M, Amini M, Nasri M, Iraj B. Area under the curve during OGTT in first-degree relatives of diabetic patients as an efficient indicator of future risk of type 2 diabetes and prediabetes. *Clin Endocrinol (Oxf)* 2017; **87**: 696-705 [PMID: 28793372 DOI: 10.1111/cen.13443]