

## **Gestational Diabetes in a High-Risk Population: Perinatal Outcomes with Impaired Fasting Plasma Glucose**

**Tarik Y. Yamani Zamzami, MD, CABOG**

*Department of Obstetrics and Gynecology, Faculty of Medicine  
King Abdulaziz University, Jeddah, Saudi Arabia  
tarikyamani@hotmail.com*

*Abstract.* The aim of the study was to compare the perinatal outcomes of gestational diabetic patients with normal fasting plasma glucose level <5.3 mmol/L, versus impaired fasting plasma glucose level  $\geq 5.3$  mmol/L on 100g oral glucose tolerance results. All gestational diabetic patients enrolled in the study were diagnosed by standard 100g oral glucose blood samples. Based on oral glucose tolerance results, patients were divided into two groups according to the fasting plasma glucose; Group 1 normal fasting plasma glucose <5.3 mmol/L, and Group 2 impaired fasting plasma glucose  $\geq 5.3$  mmol/L. During the study period, a total of 292 patients were identified as having gestational *diabetes mellitus*. One hundred eighty-two (62.3%) were with normal fasting plasma glucose <5.3 mmol/L and 110 (37.7%) patients had impaired fasting plasma glucose  $\geq 5.3$  mmol/L. The percentage of total and primary cesarean delivery and the arithmetic means  $\pm$ SD of all fasting and postprandial plasma glucose measurements were significantly lower in-Group 1 compared with Group 2 patients. Patients with impaired fasting plasma glucose needed more insulin therapy and were associated with a higher rate of cesarean delivery compared to patients with normal fasting plasma glucose who may need ordinary follow-up rather than frequent surveillance.

*Keywords:* Fasting plasma glucose, Macrosomia, Cesarean delivery, and Gestational *diabetes mellitus*.

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Correspondence & reprint request to: Dr. Tarik Y. Yamani Zamzami  
P.O. Box 80215, Jeddah 21589, Saudi Arabia

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## Introduction

Perinatal mortality among the infants of mothers with gestational *diabetes mellitus* has been reduced to the rate that is not totally different than that of the general non-diabetic population<sup>[1-3]</sup>. Improved perinatal care has prevented such increase in perinatal mortality. On the other hand, maternal and perinatal morbidity continue to be high. Uncontrolled hyperglycemia of the gestational *diabetes mellitus* (GDM) is associated with increased macrosomia and operative delivery<sup>[4]</sup>. In addition, long-term studies have shown that patients with GDM have an increased risk of developing non-insulin-dependent *diabetes mellitus*<sup>[5]</sup>. The GDM diagnosis encompasses a heterogeneous spectrum of glucose intolerance. There is insufficient data on impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), and in most studies, IFG was included under IGT. Therefore this study was undertaken to determine the perinatal outcomes of gestational diabetic patients with normal fasting plasma glucose level < 5.3 mmol/L vs. impaired fasting plasma glucose  $\geq$  5.3 mmol/L using 100g oral glucose tolerance (OGTT).

## Material and Methods

This was a prospective observational study that was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between January 1, 2003 and December 31, 2004. During the study period, all patients attending the obstetric antenatal clinic at King Abdulaziz University Hospital, a tertiary referral center, who had one or more risk factors were screened and subjected to a diagnostic test for GDM using the 100g OGTT. Maternal risk factors for GDM included: family history of diabetes, previous large baby  $\geq$  4000g, previous stillbirth or infant with congenital anomaly, obesity and history of recurrent pregnancy loss. The 100g OGTT was performed in the morning after an overnight fast of at least 8 hours (h) but not longer than 14h and after at least 3 days of diet containing greater than 150g of carbohydrates. After the ingestion of 100g of glucose, the patients were instructed to remain seated and to not eat, drink, or smoke. The results were interpreted according to the recommendation of the American Diabetic Association (ADA), who proposed the adoption of the Carpenter and Coustan criteria for diagnosis of GDM<sup>[6-7]</sup>. Patients with GDM diagnosis, when  $\geq$  2 abnormal values of the following venous plasma concentrations were met or exceeded: fasting  $\geq$  5.3 mmol/L; 1 h  $\geq$  10 mmol/L; 2 h  $\geq$  8.6 mmol/L; 3 h  $\geq$  7.8

mmol/L. The inclusion criteria for the study were: 1) Singleton pregnancy, 2) patient having GDM diagnosis, 3) patient's regular attendance to the obstetric clinic, 4) minimal follow-up with fasting and 2h postprandial plasma glucose levels. Exclusion criteria were: 1) multiple gestation and 2) *diabetes mellitus* [fasting plasma glucose level (FPG)  $\geq 7$  mmol/L, or 2-h post-load glucose 11.1 mmol/L], 3) Incomplete data records. The GDM patients were divided into two groups according to 100g OGTT results; Group 1 normal fasting plasma glucose  $< 5.3$  mmol/L, and Group 2 impaired fasting plasma glucose  $\geq 5.3$  mmol/L. The aim of glycemic control was to maintain all fasting plasma glucose values  $< 5.3$  mmol/L ( $< 95$  mg/dl) and all 2h postprandial  $< 7.8$  mmol/L ( $< 140$  mg/dl). In case of GDM diagnosis, patient was informed and started on gestational diabetic diet after referral and counseling with dietitian. If the glycemic metabolic control (fasting and 2 h postprandial plasma glucose levels) was not achieved on diabetic dietary regimen alone, patients were admitted to the hospital for 24-h glucose profile (fasting and 2h postprandial; breakfast, lunch, supper). An insulin injection was then added to control blood glucose levels. For diabetic purposes the pregnant patients were seen a minimum of once every two weeks, and with each follow-up visit a fasting and 2h postprandial plasma glucose levels performed. Usually, the purpose of re-admissions was either for obstetric reasons and/or control of blood glucose levels. The predictive variables that were likely to influence fetal outcome were noted. Maternal characteristics showed in Table 1.

**Table 1. Maternal data on both groups.**

Variable	Group 1 (n=182)	Group 2 (n=110)	p Values
Age	24.2 $\pm$ 10.6	25.5 $\pm$ 11.1	NS
Parity	5.1 $\pm$ 2.6	5.2 $\pm$ 2.7	NS
BMI	30.1 $\pm$ 6.1	31.3 $\pm$ 5.3	NS

BMI= Body mass index, Data are given as means  $\pm$  SD

The gestational age (based on last menstrual period and or ultrasound measurements) at the diagnosis and delivery of GDM patients, mode of treatment and the arithmetic means of all fasting and 2h postprandial plasma glucose values prior to delivery presented in (Table 2). After delivery, the following outcome measures were recorded: fetal birth weight,

macrosomic baby  $\geq 4000\text{g}$ , cesarean delivery, and perinatal mortality and morbidity (Table 3). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), Version 11, for Windows as appropriate. The percentage (%) or means  $\pm$ SD, “Student’s” *t*-test for continuous variables, and Chi-square test or Fisher exact test for categorical data were used. Odd ratio (OR) and the 95% confidence intervals (CI) were computed. Further, to address the effects of confounding variables of macrosomia (maternal age, parity, body mass index, and gestational delivery weeks), multiple logistic regression analyses were performed. A *p* value  $< .05$  was considered as statistically significant.

**Table 2. Gestational age diagnosis, delivery weeks, treatment and degree of glycemia control on both groups.**

Variable	Group 1 (n=182)	Group 2 (n=110)	p Values
GTT performed (Weeks)	27 $\pm$ 8.2	23.5 $\pm$ 9.1	NS
Delivery weeks	38.4 $\pm$ 2.0	38.5 $\pm$ 1.3	NS
Treatment:			
Diet	145 (79.7 %)	66 (60 %)	0.0001
Insulin	37 (20.3 %)	44 (44 %)	0.0001
Mean FPG	4.7 $\pm$ 0.5	6.6 $\pm$ 2.0	0.0001
Mean-2h PP PG	6.6 $\pm$ 1.4	8.1 $\pm$ 2.3	0.0001

*Data are given as means  $\pm$  SD and % as appropriate. FPG; fasting plasma glucose, 2-h PP PG; 2-h postprandial plasma glucose*

## Results

During the study, period a total of 292 patients met the inclusion criteria. One hundred eighty-two (62.3%) with N-FPG  $< 5.3$  mmol/L and 110 (37.7%) patients having I-FPG  $\geq 5.3$  mmol/L. The maternal characteristics (age, parity, body mass index) of both groups were comparable and not statistically significant (Table 1).

The gestational age at the diagnosis of GDM and time of delivery weeks on both groups were also statistically not different. Majority of patients Group 1 need only diet control (80%) vs. (60%) in - Group 2 (OR 1.3, 95%; CI 1.1-1.6; *p*. 0.0001). Whereas Group 2 (44% vs. 20%) required more insulin treatment, (OR 2.6 95% CI 1.6-4.4; *p* 0.0001), and

with less in-Group 1, respectively (Table 2). Regarding the metabolic control of glycemia for GDM patients, the mean  $\pm$ SD concentrations of fasting and postprandial plasma glucose measurements were significantly lower in-Group 1 compared with Group 2 ( $p$  0.0001).

The outcome of pregnancy for both groups is presented in Table 3. The percentage (%) of total and primary cesarean delivery is higher in Group 2 and it is statistically different. The mean  $\pm$ SD fetal birth weight was heavier in Group 2 and also the macrosomic babies were not statistically significant when compared to Group 1. Within each group, a logistic regression analysis model was run with the predictive variables as independent variables and each of the outcome measures as dependent variables. The results showed that Group 2 patients with impaired fasting plasma level  $\geq$  5.3 mmol/L have a significant positive effect on birth weight ( $p$  = 0.04). None of the other predictive variables appeared to be independently have a significant effect on any of the studied outcome measures.

**Table 3. Outcome measures of both groups.**

Variable	Group 1 (n=182)	Group 2 (n=110)	<i>p</i> Values
Mode of Delivery			0.002
Vaginal Delivery	157 (86.3 %)	79 (71.8 %)	
Total Cesarean Section	25 (15.3 %)	31 ( 28.2 %)	
Primary CS	14 (7.7 %)	16 (14.5 %)	
Fetal Distress	3 (1.7%)	10 (9.1%)	
Failure to Progress	11 (6.0%)	6 (5.4%)	
Fetal Weight (g)	3373.4 $\pm$ 580.3	3477.1 $\pm$ 542.9	NS
Macrosomia	21 (11.5%)	17 (15.5 %)	NS
AS < 5 at 1 minute	7 (3.8%)	3 (2.7%)	NS
AS < 5 at 5 minute	2 (1.1%)	1 (0.9%)	NS
Hypoglycemia	2 (1.1%)	3 (2.7%)	NS
SCBU		1 (0.9)	

Data are given as means  $\pm$  (S.D) and % as appropriate. Cesarean section, Macrosomia; baby weight  $\geq$  4000 g, AS; Apgar score, SCBU; special care baby unit.

The Apgar score < 5 at 1 and 5 minutes and hypoglycemia were statistically not different in both groups. There was one newborn admission to special care baby unit (SCBU) in Group 2 and there was no prenatal mortality in either groups.

## Discussion

There is insufficient evidence to recommend routine screening for GDM<sup>[8,9]</sup>. The randomized control trials documenting improvement of perinatal mortality and morbidity as a result of routine screening are lacking<sup>[10,11]</sup>. Santini *et al.* have reported that routine screening failed to decrease the rate of macrosomia (10.5% in the unscreened group vs. 11.2% in the screened group) and also, was associated with more intensive surveillance during pregnancy and a higher rate of cesarean delivery (21% vs. 26.7%;  $p < 0.01$ )<sup>[12]</sup>. Similarly, selective screening is not without problems. Coustan *et al.* showed in a population-based study that one-third to one-half of patients with gestational diabetes would be missed by the selective screening approach<sup>[7]</sup>. One may conclude that the best description of the current state of the knowledge regarding screening pregnant patients for GDM is uncertainty. There is still no consensus on practices of obstetricians to screen or diagnose GDM.

The diagnosis of GDM is so controversial that the American Diabetes Association and the American College of Obstetricians and Gynecologists support different criteria for its diagnosis. Carpenter and Coustan criteria were used. Magee *et al.* reported 50% more cases of gestational diabetes were identified, with the use of the Carpenter and Coustan thresholds, which is the more inclusive for the GDM diagnosis<sup>[13]</sup>.

The advantages of using FPG are: it is not affected by gestational age, it is similar in different ethnic patients, and that it has less variability and better reproducibility<sup>[14]</sup>. When the FPG level of the OGTT was taken into consideration ( $< 5.3$  vs.  $\geq 5.3$  mmol/L), two different populations could be distinguished with the same diagnosis. They were not only different in their glycemic response during the OGTT, but their metabolic glycemic control of the means  $\pm$ SD of fasting and 2 h postprandial level measurements during follow-up prior to delivery was significantly lower in Group 1. Furthermore, the majority of GDM patients in Group 1 were managed by diet regimen and required less insulin (OR 2.6 95% CI 1.6-4.4;  $p$  0.0001). This means some difference on the perinatal outcome measures expected, mainly incidence of macrosomia and cesarean delivery. Although, in Group 2 the fetal birth weight was greater than that of Group 1, the percentage of macrosomic babies 15.5% vs. 11.5% (OR 0.8 95 % CI 0.4-1.4;  $p$  0.2) was also not

statistically different. It may be that blood glucose level is a marker of a metabolic state associated with higher risk, rather than the direct cause of complications. Similar results have been observed by some authors who have found that after adjusting for maternal age, parity, and maternal body weight there was no correlation between blood glucose level and neonatal birth weight<sup>[3,15,16]</sup>. A Naylor *et al.* study reported that cesarean sections were more common in patients diagnosed as having GDM and it was seen in those with no macrosomia<sup>[17]</sup>. Nevertheless, the primary cesarean delivery in Group 2 (14.5% vs. 7.7%) was almost double that of Group 1 ( $p = 0.002$ ).

GDM is defined as “carbohydrate intolerance of variable severity with onset during pregnancy with return to normal after delivery”<sup>[6]</sup>. There is no threshold that clearly distinguishes between low-risk and high-risk GDM patients. Nasrat *et al.* reported that the defining of the GDM according to the severity of glucose intolerance should be emphasized<sup>[18]</sup>. The study results showed that Group 2 patients with impaired fasting plasma level  $\geq 5.3$  mmol/L have significant positive effect on birth weight ( $p = 0.04$ ). Recently, Nordin *et al.* found impaired fasting glucose level which appeared as an important predictor for increased risk of maternal/fetal morbidity<sup>[19]</sup>. Also, Lin *et al.* found that the fasting glucose value for 100g OGTT is an independent risk factor and more than three abnormal glucose values offer good diagnostic efficacy in predicting postpartum glucose intolerance<sup>[20]</sup>.

Patients with N-FPG  $< 5.3$  mmol/L during 100g OGTT are better classified as lesser degrees of glucose intolerance or mild gestational hyperglycemia (MGH)<sup>[18-19]</sup>. Furthermore, in long-term post delivery follow-up the risk of the development of abnormal GTT is significantly small<sup>[21]</sup>. A study involving a large number of patients is needed for documenting the performance of impaired fasting plasma glucose patients to predict perinatal outcomes. Furthermore, it is protocol to perform OGTT in these patients at 6 weeks postnatal, but unfortunately, due to the incompletion of patients and a lack of follow-up, these results were unavailable.

For those patients with multiple risk factors, a screening and diagnosis for GDM should be offered. Those patients with abnormal OGTT, including impaired fasting plasma glucose should be considered as having a severe form of GDM which implies a pathological state of

glucose intolerance, *i.e.* an impaired ability of  $\beta$ -cells to further increase insulin secretion in response to glucose; such diagnosis needs intensive clinical monitoring and more aggressive insulin therapy to achieve normal birth weight. Whereas, patients with normal fasting plasma glucose  $< 5.3$  mmol/L may need ordinary follow-up rather than frequent surveillance.

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## مرضى سكري الحمل في عينة سكانية عالية الخطورة: نتائج فترة ما حول الولادة عند وجود معدل غير طبيعي لعينة صيام البلازما جلوكوز

طارق يوسف يماني الزمزمي

قسم أمراض النساء والتوليد، كلية الطب، جامعة الملك عبدالعزيز

جدة - المملكة العربية السعودية

المستخلص. الهدف من هذه الدراسة هو مقارنة نتائج فترة ما حول الولادة، عند وجود معدل طبيعي لعينة صيام بلازما الجلوكوز عند المستوى  $< 5,3$  ملي مول/لتر، مقابل معدل غير طبيعي لعينة صيام بلازما الجلوكوز عند المستوى  $\geq 5,3$  ملي مول/لتر.

تم تشخيص جميع مرضى سكر الحمل اللاتي فحصن خلال الفترة الدراسة، واستنادًا إلى النتائج، تم تقسيمهما إلى مجموعتين وفقًا لمعدل مستوى عينات صوم بلازما الجلوكوز؛ المجموعة (١)  $< 5,3$  ملي مول/لتر، المجموعة (٢)  $\geq 5,3$  ملي مول/لتر.

خلال فترة الدراسة كان هناك ٢٩٢ مريضة تم تشخيصهن بمرضى سكري الحمل. مائة واثنان وثمانون (٦٢,٣٪) المجموعة (١)، و ١١٠ (٣٧,٧٪) المجموعة (٢). في المجموعة (١) نسبة عدد العمليات القيصرية ومتوسط القياسات لعينات الصيام وبعد الأكل للبلازما جلوكوز كانت أقل بكثير مقارنةً بالمجموعة (٢) وكانت ذو قيمةً من الناحية الإحصائية. أيضًا بالنسبة لعلاج الأنسولين المطلوب في المجموعة (١) كما هو متوقع، المرضى

أقل عددًا مقارنةً مع المجموعة (٢)، وكانت ذات قيمة من الناحية الإحصائية.

عند وجود معدل غير طبيعي لعينة صيام بلازما الجلوكوز للمرضى، فإنهن في حاجة إلى المزيد من علاج الأنسولين والمرتبطة بارتفاع معدل الولادة القيصرية مقارنةً للمرضى عند وجود معدل طبيعي لعينة صيام بلازما الجلوكوز، ويحتجن إلى متابعة عادية غير متواترة المراقبة.

