

A population-based screening for gestational diabetes mellitus in non-diabetic women in Bahrain

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BACKGROUND: Maternal hyperglycemia is considered a risk factor for fetal morbidity. Since there is a high prevalence of diabetes mellitus among the population of Bahrain, we conducted a prospective population-based study of gestational diabetes mellitus (GDM) in non-diabetic pregnant women.

SUBJECTS AND METHODS: All non-diabetic pregnant women attending antenatal clinics during January 2001 to December 2002 (n=10495) were screened for GDM during the 24th to 28th weeks of gestation. All positive subjects based on a 50-g glucose challenge test (GCT) were further evaluated by a diagnostic 75-g oral glucose tolerance test (OGTT). The birth weight of the child and post-delivery insulin resistance were monitored. The homeostasis model of insulin resistance (HOMA-IR) was used to assess insulin resistance.

RESULTS: Of 10495 non-diabetic pregnant women screened, 32.8% (n=3443) had plasma glucose ≥ 7.8 mmol/L (140 mg/dL) in the GCT. The 75-g OGTT found a prevalence of GDM of 13.5%. There were twice as many Bahrainis as expatriates. Of children born to women with GDM, 6.5% had a birth weight >4000 g. Post-delivery evaluation of insulin resistance indicated that 33% of women with GDM had a HOMA-IR value >2 .

CONCLUSION: The population of Bahrain is a high-risk ethnic group for GDM. The association of insulin resistance in the post-gravid state with GDM among 33% of the study population suggests that insulin resistance, the possible cause of the pathophysiological mechanism underlying the development of gestational diabetes, continues in the post gravid state.

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Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy.¹ GDM and obesity are common metabolic abnormalities occurring during pregnancy. Decreased maternal insulin sensitivity in women with GDM may increase nutrient availability to the fetus, possibly accounting for an increased risk of fetal overgrowth and adiposity.² Maternal hyperglycemia is considered as risk factor for fetal morbidity. Failure to diagnose and treat GDM will result in increased morbidity in some pregnancies while an aggressive approach to diagnosis and treatment may result in unnecessary intervention in others.³ The diagnostic criteria for gestational diabetes can be set to identify only very high-risk pregnancies (and miss some at-risk pregnancies) or all at-risk pregnancies (including many no-risk pregnancies). Recommendations from the Fourth International Workshop-Conference on Gestational Diabetes Mellitus in 1997 suggested a procedure for screening all non-diabetic pregnant women of average or high risk by measurement of plasma glucose between 24 to 28 weeks of gestation, using a two-step procedure.¹ Glucose tolerance deteriorates in human pregnancy, but about 97% to 98% of all pregnant women retain a normal glucose tolerance and only 2% to 3% develops GDM.⁴ Based on the National Diabetes Data Group criteria, the percentage of pregnant non-diabetic women who had GDM was 4%.⁵ Using the criteria of the Fourth International Workshop-Conference On Gestational Diabetes, the percentage of non-diabetic pregnant women having GDM increased to 7%.⁶

The higher risk of developing type 2 diabetes and hypertension in women who have a history of GDM appears to be attributable to insulin resistance.⁷ There is ample evidence

that the diabetogenicity of pregnancy is related to a pronounced peripheral resistance to insulin.⁴ Insulin concentrations are increased to about three times that seen in the non-pregnant state. Increased resistance is caused by post-insulin receptor events and is probably brought about by the cellular effects of the increased plasma levels of one or more of the pregnancy-associated hormones and free cortisol. There is evidence that resistance is predominantly located in the muscle tissue, where significant reductions in certain key enzymes in glucose and lipid metabolism have been demonstrated.⁴ Decreased maternal pre-gravid insulin sensitivity (insulin resistance) coupled with an inadequate insulin response is the pathophysiological mechanism underlying the development of gestational diabetes.² Insulin-regulated carbohydrate, lipid and protein metabolism are all affected to a variable degree. Women with GDM had higher insulin resistance, especially those who needed insulin therapy. The lipid profile in GDM was related to the level of insulin resistance.⁸ Insulin resistance and beta-cell dysfunction are thought to be major determinants of its development. Its pathophysiological mechanism in many ways resembles that of type 2 diabetes. There is an evolving body of evidence from the last decade describing similarities between GDM and the metabolic (insulin resistance) syndrome. These new observations suggest that GDM might be an early manifestation of the metabolic syndrome.⁹ Although glucose tolerance normalizes shortly after pregnancy with GDM in the majority of women, the risk of developing overt diabetes, especially type 2 diabetes is markedly increased.¹⁰ Insulin resistance and beta cell function in Asian and Caucasian women are similar. GDM in Asian women is of similar aetiology to that seen in Caucasian women, but occurs at a lower BMI.¹¹ The major causes of insulin resistance are the genetic deficiency of glycogen synthase activation, compounded by additional defects due to metabolic disorders, receptor down regulation, and glucose transporter abnormalities, all contributing to the impairment in muscle glucose uptake. The liver is also resistant to insulin in type 2 diabetes, which is reflected in persistent hepatic glucose production despite hyperglycemia.¹²

Increased frequency of congenital anomalies and stillbirth were reported as a complications of GDM.^{13,14} Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, polycythemia and hypocalcaemia have been reported in infants of women with GDM.¹⁵ Macrosomia affects 20 to 30 percent of infants whose mothers have GDM.¹⁶

In the Kingdom of Bahrain, there is a high prevalence of diabetes mellitus with most of the population having first-degree relatives with diabetes who belong to an average or high-risk ethnic group.¹ With these points in mind, we conducted a prospective, population-based study on GDM to assess the prevalence of GDM in Bahrain. A follow-up study was also conducted to assess the incidence of macrosomia and congenital anomalies among the children of women with GDM with a post-gravid status of insulin resistance 6 weeks after delivery using the homeostasis model assessment of insulin resistance (HOMA-IR).¹⁷ HOMA-IR is a useful index of insulin resistance because of its correlation with the euglycemic hyperinsulinemic clamp, the gold standard technique of measuring insulin resistance.¹⁷

Subjects and Methods

All non-diabetic pregnant women who visited antenatal clinics at health centers and at Salmaniya Medical Complex during January 2001 to December 2002 (2 years) were requested to undergo a two-step testing procedure as per guide lines of the Fourth International Workshop-Conference on Gestational Diabetes. The procedure involves two steps, the first an assessment of plasma glucose after a 50-gram oral glucose challenge test (GCT). In the second step, a diagnostic 3-hour 75 g oral glucose tolerance test (OGTT) was performed in patients with ≥ 7.8 mmol/L (140 mg/dL) of plasma glucose after the 50-g oral glucose challenge. The amount of glucose in the OGTT is 100 g in North America.²¹ The 75-g oral glucose was used as the challenge dose by the World Health Organization²² and the European Diabetic Pregnancy Study Group.²³ We used 75 g of glucose as there was less tendency toward vomiting. The cut-off values for both challenge doses were identical for fasting, and for the one-hour and two-hour values.³ The two-step testing was used as the fasting blood glucose-based screening test was not sensitive enough to determine GDM. Chilled glucose syrup with 50 g of glucose as syrup with orange flavor (manufactured by Bahrain Danish Dairy Company) was given orally and a blood sample was collected after 1 hour in a fluoride oxalate tube as step one to assess the risk of GDM. The chilled and orange-flavored glucose was preferred to decrease vomiting tendency among the pregnant women.

The subjects were advised to follow a carbohydrate diet for 3 days before testing followed by fasting for 8 to 14 h before visiting the laboratory for OGTT on the day of appointment. Blood samples

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were collected every hour for three hours in fluoride oxalate tubes. The samples were assayed for glucose in plasma from fluoride oxalate tube by the hexokinase method (Roche Diagnostics Mannheim, Germany). GDM was diagnosed by criteria based on recommendations of Fourth International Workshop-Conference On Gestational Diabetes (Table 1) taking into consideration that cut-off points for plasma glucose for the 75-g OGTT and 100-g OGTT are identical.³

The women with GDM were followed at secondary care centers and the birth weight of children after delivery as recorded in medical records was taken into consideration to evaluate macrosomia (based on a cut-off point >4000 g birth weight as per the norm followed in the Toronto Tri-Hospital Gestational Diabetes Project, 1995¹⁸). Congenital anomalies in the fetus, if any, and stillbirth recorded in medical records were also taken into consideration to identify the incidence of congenital anomalies and stillbirth in women with GDM.

Post-gravid fasting blood glucose and fasting serum insulin were assessed in the samples collected 6 weeks after delivery from those who provided samples to evaluate insulin resistance using the principle of homeostasis model assessment of insulin resistance (HOMA-IR).¹⁷ HOMA-IR is assessed as a product of fasting insulin ($\mu\text{IU/mL}$) and fasting plasma glucose (mmol/L) divided by 22.5. Serum insulin was assayed by electrochemiluminescence immunoassay method (Roche diagnostics Mannheim, Germany). All data in this study were analyzed by Stat Tools in Microsoft Excel.

Results

Of 10 495 (Bahraini, 7575; expatriates, 2920) non-diabetic pregnant women screened for GDM, 3443 (32.8%) (Bahraini, 2673; expatriates, 770) had a 50-g GCT ≥ 7.8 mmol/L (140 mg/dL), suggesting possible high risk of GDM (Table 2). Of those, 1394 (13.3% of non-diabetic pregnant women) had GDM as per criteria in Table 1. The ratio between Bahraini and expatriates among the women with GDM was 2:1 (Table 3).

The women with GDM were maintained on a regulated diet or regulated diet and insulin until delivery at secondary care centers. After delivery the birth weight of children as recorded in the medical record of each patient was taken into consideration to evaluate the incidence of macrosomia among the gestational diabetic mothers. Ninety-one children born to gestational diabetic mothers had a birth

Table 1. Criteria for diagnosis of gestational diabetes by venous plasma glucose concentration using the 75-g oral glucose challenge test (or 100 g oral glucose challenge test as cut-off values are identical) based on recommendations of the Fourth International Workshop-Conference On Gestational Diabetes.¹

Measurement	Glucose concentration in mmol/L
After overnight fasting	≥ 5.3 (95 mg/dL)
1 hour after 75-g oral glucose challenge	≥ 10.0 (180 mg/dL)
2 hours after 75-g oral glucose challenge	≥ 8.6 (155 mg/dL)
3 hours after 75-g oral glucose challenge	≥ 7.8 (140 mg/dL)

Table 2. Plasma glucose screening for gestational diabetes with the 50-g oral glucose challenge test (step one) with plasma glucose cut-off point ≥ 7.8 mmol/L based on recommendations of Fourth International Workshop-Conference On Gestational Diabetes.¹

No. of women screened	No. of women with positive screening test for gestational diabetes	Proportion of women with positive screening test
10 495 (total)	3443	32.8%
7575 (Bahraini)	2673	35.3%
2920 (expatriate)	770	26.4%

Table 3. Gestational diabetes mellitus (GDM) among step-one positives (50-g OGTT) based on diagnostic 75-g oral glucose challenge test.

No. of women subjected to OGTT based on screening test	No. of women with positive test for GDM	Proportion of women with positive test for gestational diabetes among non-diabetic pregnant women
3443 (total)	1394	13.3%
2673 (Bahraini)	1175	15.5%
770 (expatriate)	219	7.5%

weight >4000 g (based on the Toronto Gestational Diabetes Project, 1995¹⁸), suggesting a rate of macrosomia among women with gestational diabetes of 6.5% in Bahrain. Among the women with gestational diabetes, one child was born with anencephaly, and 11 women with gestational diabetes had stillbirth as a complication.

After delivery the women with gestational diabetes were assessed for post-gravid insulin resistance. Samples collected from 235 women with GDM six weeks after delivery were analyzed for serum insulin and fasting glucose. Samples could not be obtained from all patients due to difficulty in compliance. In the homeostasis model of insulin assessment (HOMA-IR), 33% had HOMA-IR >2 (Table 4).

Table 4. Post-gravid insulin resistance assessed by homeostasis model of insulin resistance (HOMA-IR).

HOMA-IR group	Mean value*	Proportion with indicated value
>2	2.7±0.3	78 (33%)
<2	1.6±0.2	157 (67%)

*Reference range in normal individuals, 1.56±0.49

Discussion

The results of this study suggest that there is a high ethnic and racial tendency toward GDM in the Bahraini population. Based on the 75-g OGTT, 13.3% of non-diabetic pregnant women had GDM, with a 2:1 ratio of Bahrainis to expatriates (15.5% vs. 7.5%). In contrast, in a group of predominately white women the prevalence of GDM was 7%.⁶ In the native population in northwestern Ontario, Canada, the prevalence of GDM was 8.4%.²⁰ The incidence of GDM is between 0.15% to 15%, which corresponds to the prevalence of type 2 diabetes and impaired glucose tolerance in a given country.²⁴ Ethnicity has been proven to be an independent risk factor for GDM, which varies in prevalence in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group. There are several identifiable predisposing factors for GDM, and in the absence of risk factors, the incidence of GDM is low.²⁵ The unmodifiable risk factors are ethnicity, pre-pregnancy weight, age, parity, family history of diabetes, and degree of hyperglycemia in pregnancy and immediately postpartum. The modifiable risk factors are persistent obesity, future weight gain, and subsequent pregnancies. Additional modifiable

risk factors in these women are likely to be levels of physical activity, dietary fat, and avoidance of other lifestyle factors that adversely influence insulin resistance, such as smoking and certain drugs.²⁶ This study has shown that the native population of the Kingdom of Bahrain is a high-risk ethnic group with a high prevalence (13.3%) of GDM, which may be directly related to the high incidence of type 2 diabetes and the presence of risk factors for GDM. Long-term measures are essential to educate the population about decreasing risk factors and to monitor women with GDM.

Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, polycythemia and hypocalcaemia were noted with varying frequencies in the infants of women with GDM.^{6,15,16} Approximately 20% to 30% of children of gestational diabetic mothers were affected by macrosomia.¹⁶ There were 11 stillbirths and one case of anencephaly. Macrosomia with a birth weight >4000 g (based on criteria of the Toronto Tri-Hospital Gestational Diabetes Project, 1995¹⁸) were noted in 6.5% of women with GDM. Measures taken to monitor women with GDM in Bahrain have played a role in this low percentage of macrosomia.

GDM and obesity are common metabolic abnormalities occurring during pregnancy. Decreased maternal pre-gravid insulin sensitivity (insulin resistance) coupled with an inadequate insulin response is the pathophysiological mechanism underlying the development of GDM.²⁻⁸ In the homeostasis model of insulin assessment (HOMA-IR), we found that insulin resistance increased in 33% of women with GDM in the post-gravid state. The association of insulin resistance in the pre-gravid state as reported in an earlier study and in 33% of women with GDM in the post-gravid state in the present study suggests a high-risk tendency for GDM in women with insulin resistance, which continues in the post gravid state. There is thus a need for assessment and monitoring of insulin resistance in these women as they have greater susceptibility to GDM. We intend to extend this study with a well-designed cohort study.

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