Prediction of glucose intolerance at 24-28 weeks of gestation by glucose and insulin level measurements in the first trimester

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ABSTRACT

Background: Gestational diabetes is the second common disorder in pregnancy period, which is detected in 24-28 weeks of gestational age through screening tests in low-risk women. The women with gestational diabetes are prone to prenatal mortality and development of future diabetes. Therefore, detection of these individuals in the first trimester and conducting preventive interventions is of great importance. This study aimed to define the predictive value of fasting plasma glucose (FPG) and fasting plasma insulin (FPI) test in first trimester concerning the positive result of oral glucose challenge test)OGCT(.

Materials and Methods: This is a prospective and observational study conducted on 88 pregnant women in Tehran. After FPG and FPI measurements in these women in the first trimester, a screening test of GCT with 50 g oral glucose was conducted in 24-28 weeks of gestational age. Diagnostic value of FPG and in these two groups of positive and normal GCT results was evaluated through receiver operator characteristic (ROC) curve. *P* < 0.05 was considered significant.

Results: In this study, 15 subjects (17%) were detected with a positive GCT result. The sub-curve area of ROC diagram for FPG and FPI was calculated to be 0.573and 0.592, respectively, which reveals that FPG and FPI cannot have a proper predictive value for the positive result of GCT. Based on the results, the best cutoff points for FPG and FPI are 79.5 mg/dl and 7.55 μIU/ml, with accuracy of 60-67% and specificity of 45.2-47%.

Conclusions: Only higher fasting glucose levels in early pregnancy, within the normoglycemic range, would predict the development of glucose intolerance with limited sensitivity and specificity.

Key words: First trimester, gestation, glucose intolerance, prediction, pregnancy

INTRODUCTION

Carbohydrate intolerance of varying severity, diagnosed or caused for the first time during pregnancy, is named gestational diabetes. There is no doubt that some of the women suffering from gestational diabetes have overt diabetes, not diagnosed before their pregnancy.[1] Gestational diabetes is the most common metabolic disorder during pregnancy, with a prevalence of 5%.[2]

Women with gestational diabetes are more prone to the risk of prenatal mortality and involvement in future

diabetes.[3] In fact, prevalence of gestational diabetes in a population reflects the prevalence of type 2 diabetes in the same population[4] A review of existing studies on the status of gestational diabetes in Iran reveals that its prevalence varies from 1.3 to 8.9%.[2] Pregnancy is a diabetogenic stage, which refers to a progressive reduction in insulin sensitivity, especially in the third trimester. Based on its biological mechanism, gestational diabetes screening is recommended between 24 and 28 weeks of gestational age.[4] To detect diabetes among pregnant women, screening in late second trimester has been recommended.[5] Now, the most acceptable screening test of glucose tolerance, i.e. the primary screening test of glucose challenge test (GCT), is conducted with 50 g oral glucose with a threshold of 140 mg/dl.[6] This test has been reported to have a detection level of 79% and a false-positive rate of 13%.[7] In individuals with a GCT positive result, diagnostic 3 h GTT test with 100 g oral glucose is conducted. Although 50 g oral glucose test is the golden diagnostic standard, due to numerous limitations of glucose monitoring with 50 g glucose, the necessity of its replacement by a more convenient, tolerable, cost-effective, reliable, repeatable,

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and non-invasive test is felt to facilitate gestational diabetes diagnosis and screening algorithm.[8] Based on recently published research, inappropriate outcomes in pregnancy like hypertension,[9] preterm labor,[10] fetal macrosomia, amniotic sac rupture, cesarean section, postpartum intolerance,[11] and future cardiovascular diseases[12] have been reported more in non-diabetic women with just an abnormal GCT, compared to pregnant women with a normal test.[13] As gestational diabetes is a progressive health problem in the world, especially in developing countries, some research has been recently conducted on the prediction power of gestational diabetes in the first trimester based on biochemical blood and plasma tests to prevent maternal complications through preventive interventions and to diminish their financial burden in the societies. Unfortunately, in most of the cases, gestational diabetes is diagnosed after the first half of the pregnancy has passed through either a two-step or a one-step screening.[14] Therefore, as interventions such as diet, prescription of medication, sports, and regular blood glucose monitoring are conducted earlier in pregnancy and can potentially reduce the progression of gestational diabetes and its negative outcomes, early detection of women predisposed to the risk of diabetes in early pregnancy is ideal.[15,16]

Research reports that changes in fasting plasma glucose (FPG) and fasting plasma insulin (FPI) levels in the first trimester can be used to detect pregnant women who finally develop gestational diabetes.[3]

Measurement of these parameters is conveniently conducted, and is tolerable, reliable, repeatable, and cost-effective.[17] If this measurement is capable of prediction of diabetes in late pregnancy, it can diminish progressive increase in negative outcomes of diabetes. Despite increased usage of FPG and FPI measurements in screening of gestational diabetes, their application has yielded controversial results in various populations.[3,17,18] In addition, most of the studies have been conducted on the ability of FPG test in detection of gestational diabetes, parallel to screening tests in the second trimester. Agarwal *et al.*, in their study on the utility of FPG as a screening test, reported that based on the diagnostic criterion of American Diabetes Association (ADA), FPG has a diagnostic efficiency in diagnosis of gestational diabetes. They concluded in another article that fasting capillary glucose threshold of 84.6 mg/dl in the second trimester with sensitivity of 86% can reduce 75 g glucose tolerance test among the pregnant women by 50%.[19,20] On the other hand, Reicheit, in a study on FPG test as a useful test to diagnose gestational diabetes, concluded that fasting glucose threshold of 85 mg/dl with a sensitivity and specificity of 86% is an acceptable criterion in detection of gestational diabetes.[21] With regard to disagreement on the

time of FPG test in screening of gestational diabetes, this study aimed to determine the prediction value of FPG and FPI levels in the first trimester concerning the gestational diabetes screening in the second half of pregnancy.

MATERIALS AND METHODS

This is a prospective observational study. The number of the subjects was calculated as 88 by 95% confidence of 1.96, 80% test power of 0.84, and SD error rate of 0.84. Study population included all pregnant women whose first referral for prenatal care was before the gestational age of 12 weeks and who were referred to Azadi midwifery clinic and National Oil Company hospital in Tehran to receive routine prenatal care during the period December 2012-January 2013.

Inclusion criteria were: Iranian women aged 20-35 years, body mass index (BMI) 19-25 kg/m^2, singleton pregnancy, no glycosuria in their first referral before the gestational age of 12 weeks, taking no medication, no problem in the present pregnancy needing a special care, and generally, being in a low gestational diabetes risk group (no history of diabetes in the subject and her immediate relatives, no macrosomic infant, stillbirth, abortion, and polyhydramios in previous pregnancies). Exclusion criteria were: subjects not referring to the laboratory which was allocated by the researcher, FPG >95 mg/dl and with multiple pregnancy detected in the next stages, not referring for a follow-up visit, loss of interest to cooperate with the study, incomplete or missing test results, and a need for pregnancy termination due to any reason before the gestational age of 24 weeks. Data were collected through evaluation of plasma glucose and insulin biochemical parameters and measurement of subjects' weight and height. These data were recorded in a data recording note containing four sections by the researcher. The first section contained mothers' demographic characteristics. The second section contained 10 questions on subjects' present pregnancy, and the third section included seven questions on previous pregnancies and diseases. Finally, in the fourth section, the test results were recorded. After obtaining an approval from ethics committee of Isfahan University of Medical Sciences, the researcher referred to research environment and explained the research goals to the women meeting the study inclusion criteria and referring to receive prenatal care at 8-12 weeks of gestational age. In the end, sampling was conducted after obtaining an informed written consent and subjects' reliance. Firstly, a urine test was requested to detect glycosuria, and if negative, the subjects were introduced to the same laboratory in the clinic to have other maternal routine tests, especially FPG and FPI, and the test results were recorded in their files. Subjects with an FPG level of

<95 mg/dl were considered for participation in the study, and the women with FPG over that value were excluded from the study and recommended to have special care by the related specialist. All subjects underwent a screening test with 50 g glucose at gestational age of 24-28 weeks in the same laboratory. Blood glucose monitoring and oral glucose tolerance test were conducted using glucose oxidase kit and Hitachi 902 autoanalyzer through photometry method. FPI was measured by Diaplas kit and STSTFAX 303 device through enzyme-linked immunosorbent assay (Elisa) method in the National Oil Company hospital. The subjects whose 1-h blood glucose level was ≥140 mg/dl after taking 50 g glucose were considered as those with negative screening test result. The results of subjects' glucose and insulin tests in the first trimester were reviewed after obtaining the results of the screening test conducted in the second trimester. Through use of these data, insulin resistance index Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by multiplication of FPG values (mg/dl) by FPI (μIU/ml) divided by 405. Data were analyzed by independent *t*-test and receiver operator curve (ROC). $P < 0.05$ was considered significant.

RESULTS

In the present study, 88 subjects underwent GCT with 50 g of glucose, of whom 73 subjects (83%) had GCT <140 mg/dl and 15 (17%) had GCT ≥140 mg/dl. About 53.4% of the subjects had high school education and 93% were homemakers. Women's mean age in normal and positive GCT result groups were 28.19 (3.39) and 28.9 (3.61) years, respectively.

Independent *t*-test showed no significant difference in age in the two groups ($t = 0.07$). Mean primary BMI in normal and positive GCT groups were 21.90 (1.65) and 22.20 (2.04), respectively. Despite higher BMI found in positive GCT women, independent *t*-test showed no significant difference ($t = 0.6$). Mean ranks of pregnancy and delivery in normal and positive CGT groups were 1.79 (0.83) and 0.63 (0.63), and 1.8 (0.56) and 0.67 (0.61), respectively. Independent *t*-test showed no significant difference in pregnancy and delivery ranks in the two groups ($t = 0.2$). Mean FPG levels at 8–13 weeks of gestation in normal and positive GCT groups were 80.48 (8021) and 82.80 (9.3), respectively. Despite a higher level of FPG found in positive GCT group, independent *t*-test showed no significant difference ($t = 0.97$) [Table 1]. ROC was calculated as 0.573 for the prediction ability of FPG [Figure 1]. Based on this curve, the best cutoff point for FPG was 79.5 mg/dl with a sensitivity of 60% and specificity of 45.2%. The obtained positive and negative predictive values were 18.4% and 84.6%, respectively. In the present study, mean FPG values obtained in normal and positive GCT groups were

Table 1: Comparison of the means of variables in two groups of normal and positive GCT

Group	GCT<140		GCT≥140		Independent *t*-test	
Variable	Mean	SD	Mean	SD	t	P
Age	28.19	3.39	28.27	3.61	0.07	0.93
BMI	21.90	1.65	22.20	2.04	0.6	0.55
Pregnancy rank	1.79	0.83	1.8	0.56	0.07	0.98
Delivery rank	0.63	0.63	0.67	0.61	0.2	0.83
FPG	80.48	8.21	82.80	9.29	0.97	0.33
FPI	11.65	7.11	8.92	4.6	1.41	0.15
HOMA-IR	2.34	1.5	1.85	1.07	1.19	0.23

BMI: Body mass index, SD: Standard deviation, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, GCT: Glucose challenge test, HOMA-IR: Homeostasis model assessment of insulin resistance
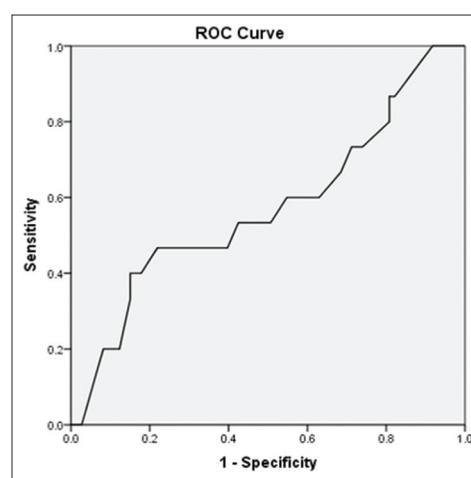

Figure 1: ROC sub-curve area for the ability of FPG in prediction of positive GCT.

11.65 (7.11) and 8.92 (4.6), respectively. Mean FPI levels in the two groups of normal and positive gestational diabetes screening test showed no significant difference ($t = 1.41$). It was notable that mean FPI in positive GCT group was less than in normal GCT group. ROC for FPI prediction ability was 0.592 [Figure 2]. Based on this curve, the best cutoff point for FPI was obtained as 7.55 mg/dl with a sensitivity of 67%, specificity of 47%, positive predictive value of 22.6%, and negative predictive value of 86%.

Mean insulin resistance obtained in normal and positive GCT groups were 2.34 (1.5) and 1.85 (1.07), respectively. In the present study, there was no significant difference in mean insulin resistance in normal and positive gestational diabetes screening test groups ($t = 1.19$).

DISCUSSION

Vast research has been conducted to find more cost-effective and convenient methods such as FPI and FPG tests to replace GCT.[22] Most of the studies have
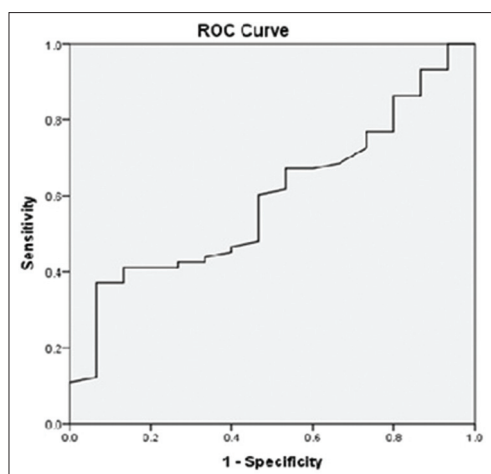
Figure 2: ROC sub-curve area for the ability of FPI in prediction of positive GCT

investigated FPG or even capillary glucose at the beginning of the third trimester and concurrent with oral glucose challenge test (OGCT) and oral glucose tolerance test (OGTT) at 24-32 weeks of gestation,[19,20,21] while a few have evaluated FPG and FPI in the first prenatal visit. [4,23-25] Only two studies have investigated the effect of chemical tests of the first trimester on prediction of glucose tolerance disorder. All pregnant women (low risk and high risk), except those with a known disease in their present or previous pregnancies, referring to the centers for prenatal care participated in the study. The present study is the only study that has worked on these issues among women with no risk factor of gestational diabetes. Kashanizadeh *et al.*, in a study on evaluation of the effect of 50 g glucose tolerance test on diagnosis of gestational diabetes in women with no risk factor, reported that about 20.3% of the women who finally showed a glucose tolerance disorder belonged to low-risk group of the disease, which is an acceptable percentage and reveals the necessity of more attention to be paid to this group.[26] This study was conducted to investigate the predictive value of FPI and FPG in relation to glucose tolerance disorder found on gestational diabetes screening in the first trimester among low-risk pregnant women of Tehran. In the present study, positive GCT with a cutoff of ≥140 mg/dl was found in 17%, which is consistent with the reported prevalence in the scientific texts and references,[27] Kashanizadeh's study (20%), and Yachi's study (20.8%).[3,26] With regard to consideration of specific inclusion criteria to lower the confounding factors effective on diabetes involvement, lack of any significant difference in the groups concerning age, BMI, pregnancy, and delivery rank seems normal. In the present study, FPG level ≥79.5 mg/dl with a sensitivity of 60% and specificity of 45.2% was obtained as the best threshold for prediction of positive GCT. Positive predictive value of this test was found to be 18.4% and its negative

predictive value was 84.6%. ROC was used to check the prediction value of this criterion for glucose tolerance test disorder.

The sub-curve area for FPG in prediction of positive GCT result was calculated as 0.573, which shows that FPG cannot have a proper predictive value in positive GCT result. In Yachi's study, ROC sub-curve area for the value of FPG in prediction of positive GCT result was obtained as 0.588, which suggests that FPG level alone cannot be a proper predictive factor for positive GCT.[3] Our results showed that mean FPG in the group of positive gestational diabetes screening test was higher, compared to the normal gestational diabetes screening test group, although the difference was not significant. Yachi, in a study on the role of FPG level in prevalence of glucose intolerance in the first trimester, reported that mean FPG in the group of positive GCT was more than in normal GCT group.[3] Lopez Caudana, in a study on the predictive value of glucose and insulin measurements in glucose metabolism in the first trimester, found out that FPG level determines the possibility of women's involvement in glucose intolerance and gestational diabetes.[4] He determined an FPG level of 77.5 mg/dl with a sensitivity of 70% as the best cutoff point for fasting glucose in detection of positive GCT, which is consistent with the present study. Yachi, in his study, reported that fasting glucose level of 65.8 mg/dl with a sensitivity of 86% and specificity of 29% is the best cutoff point. With regard to its very low specificity (29%), he suggests to use other complementary tests such as FPI to enhance its efficiency. In the present study, positive predictive value of 14.8% in FPG test in detection of the probability of women's glucose intolerance makes the use of other complementary tests logical. In the present study, ROC sub-curve area for FPI's ability in prediction of positive GCT was 0.592, which means that FPI cannot have a proper predictive value for positive GCT result. Based on this curve, the best cutoff point for FPI was obtained as 7.55 µIU/ml with an accuracy of 67%, specificity of 47%, positive predictive value of 22.6%, and negative predictive value of 86%.

Lopez Candana, in his research, after groups' homogenization concerning age and BMI, explains that high levels of FPG (81-123 mg/dl) are accompanied with a higher risk of glucose intolerance incidence and gestational diabetes, and that women with moderate or high plasma insulin levels (5.93-26.53 µIU/ml) and high insulin resistance (HOMA-IR) (1.8-5.7) are just predisposed to gestational diabetes, and there is no association between insulin level and glucose intolerance incidence.[4] Grewal reports that FPI >7.45 µIU/mg can predict the progression toward diabetes with a sensitivity of 80%, specificity of 57.4%, and negative predictive value of

97%. He argues that hyperinsulinemia in the first trimester occurs within 24-28 weeks of gestation and before the incidence of hyperglycemia, and predicts the progression of gestational diabetes with limited accuracy and specificity. He adds that after groups' homogenization concerning age and BMI, no significant difference was observed between groups.[24] Based on the reviewed studies, it can be inferred that BMI is a very important factor in the incidence of insulin resistance and sensitivity, especially in early pregnancy. Catalane concluded that obese or overweight women are at a higher risk of insulin sensitivity reduction and, consequently, there is increased stimulation of beta cells in pancreas for secretion of insulin and increase in insulin resistance index.[28] In a similar article, Lapolla studied early diagnosis of late gestational disorders through an investigation on beta cells' function and the level of insulin sensitivity in early pregnancy. He found that these indexes were not capable of revealing insulin sensitivity disorder in the women with normal BMI, who finally developed gestational diabetes mellitus (GDM). He argues that among women with GDM and normal weight, those who manifested GDM in earlier stages showed more defect in insulin secretion, compared to those who developed GDM in later stages.[25] In the present study, as the pregnant women had normal range of BMI, mean FPI obtained in women with glucose intolerance disorder was less than in normal group.

CONCLUSION

The results obtained in the present study show that increase in FPG more than our obtained threshold in the first trimester, which was in normal range, can predict the probability of glucose intolerance with limited accuracy and specificity and, more importantly, can help healthcare providers, especially midwives who are in touch with the pregnant women more, and reduce glucose intolerance disorder and its related complications and follow-ups in women with FPG >79.5 mg/dl through nutritional and sport recommendations.

With regard to our obtained statistical results, further studies with higher number of subjects and for a longer duration are recommended. Complementary FPI test in the first trimester in women with normal BMI is not helpful in increasing the prediction value of glucose intolerance disorder.

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