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Prediction of gestational diabetes mellitus in a high-risk group by insulin measurement in early pregnancy

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Abstract

Aims We hypothesized that an increased serum insulin level in early pregancy reflects an increased demand on the compensatory capacity of the pregnant woman, and can serve as a predictor of gestational diabetes mellitus (GDM).

Methods A 2-h, 75-g oral glucose tolerance test (OGTT), with fasting and 2-h postprandial serum insulin determination, was performed in 71 pregnant women with one or more risk factors for GDM before gestation week 16. In 64 patients, subsequent OGTTs were performed at gestation weeks 24–28, and in the event of a negative result, at gestation weeks 32–34.

Results Insulin determination at fasting and at 120 min had sensitivities of 69.2% and 92.3%, and specificities of 96.4% and 85.7%, respectively, for the prediction of GDM at gestation weeks 24–28. The sensitivities decreased to 33.3% and 75.0%, respectively, for the prediction of GDM at gestation weeks 32–34. Insulin determination at fasting and at 120 min had positive predictive values of 0.90 and 0.75, respectively, for the prediction of GDM at gestation weeks 32–34. The negative predictive values of fasting and 120-min serum insulin determination at gestation week ≤ 16 were 0.87 and 0.96, respectively, for the prediction of GDM at gestation weeks 24–28. Increased serum insulin levels both at fasting and 120 min before gestation week 16 were very strong predictive factors for GDM by gestation weeks 32–34 with an odds ratio of 16.6 and 13.3, respectively.

Conclusions Serum insulin determination at gestation week ≤ 16 is an easy and reliable method with which to predict GDM in a high-risk group. Despite a negative OGTT, patients with an elevated fasting and/or 120-min serum insulin level at gestation week ≤ 16 should be managed in the same way as those with GDM. Considering the very high negative predictive value of the method, patients with a normal fasting and/or 120-min serum insulin level at gestation week ≤ 16 should undergo an OGTT only at gestation weeks 32–34.

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Keywords diagnosis, gestational diabetes mellitus, insulin, risk factors, screening

Abbreviations BMI, body mass index; GDM, gestational diabetes; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test

Introduction

Changes in hormonal status, insulin resistance, physical activity and food intake result in an approximately two- to three-fold increase in insulin requirement during pregnancy, starting from weeks 16–18 of gestation. These physiological changes lead to gestational diabetes mellitus (GDM) when the insulin

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requirement exceeds its secretion. Although GDM can develop at any time during pregnancy, depending on the compensatory capacity of the pregnant woman, it most often develops in the third trimester, as the insulin requirement is the highest at that time [1].

It is recommended that those patients with risk factors for GDM, such as a family history of diabetes, a history of an adverse perinatal outcome (macrosomia, malformation, polyhydramnios, stillbirth or missed abortion), a maternal age > 35 years, obesity, hypertension or glycosuria, undergo screening at the first prenatal visit [2–4]. Subsequent testing is recommended at gestation weeks 24–28 if the screening in early pregnancy yields a normal result. However, a negative oral glucose tolerance test (OGTT) with an increased fasting and/or postprandial serum insulin level reflects an increased demand on the compensatory capacity of the pregnant woman. We hypothesized that an increased serum insulin level at screening in early pregancy can predict GDM.

The aim of this study was to determine the predictive value of the serum insulin level before gestation week 16 in a high-risk group in the identification of subsequent GDM.

Methods

This prospective observational study was carried out between 1 January 2001 and 28 February 2002. The study protocol was approved by our local ethics committee. All pregnant women referred to our special Diabetic Pregnancy Outpatient Department who displayed one or more risk factors for GDM (n = 90) were enrolled in the study after informed consent. Nineteen of the 90 patients were excluded from the study as they were referred to our department after gestation week 16 or had had GDM in a previous pregnancy. The pregnant women who had had GDM in a previous pregnancy were managed as patients with pregestational diabetes mellitus. After their informed consent had been given, a 2-h, 75-g OGTT was performed in 71 pregnant women before gestation week 16 according to the World Health Organization (WHO) criteria with serum insulin determination at fasting and at 2 h [5,6]. The pregnant women were instructed to consume at least 150 g carbohydrate/day for 3 days and to fast overnight for 10–12 h on the day before the OGTT. Plasma glucose and insulin levels were obtained by repeated venepuncture at fasting and 120 min after ingestion of a 75-g glucose solution over 5 min. Glucose levels were determined by the GOD-POD (glucose oxidase–peroxidase) colorimetric method (RANDOX Laboratories Ltd, Crumlin, UK) on venous blood collected into sodium fluoride. Both the inter-assay and the intra-assay coefficients of variation (CV) were < 2%. Patients were considered to have GDM in the event of a glucose level of ≥ 7.0 mmol/l at fasting and/or of ≥ 7.8 mmol/l at 120 min, according to the WHO criteria. Seven patients were excluded from further analysis as GDM was diagnosed in this first OGTT before gestation week 16. Serum insulin levels were determined by chemiluminescent immunoassay (DPC Immulite 1000; Diagnostic Products Co., Los Angeles, CA, USA), with an interassay CV of 7.6% and an intra-assay CV of 4.8%. This method has a cross-reaction with proinsulin of 8.5% and has no cross-reaction with C-peptide and glucagon as stated in the original description of the method. Serum insulin levels of ≥ 30 mU/l at fasting and ≥ 70 mU/l at 120 min were considered to be hyperinsulinaemic based on our laboratory reference ranges for a population of body mass index (BMI) ≥ 27 kg/m^2, which are similar to the values given in the protocol description of Immulite and to that described by Ascaso *et al.* in an obese non-pregnant population [7] with normal glucose metabolism. Subsequent OGTTs without insulin determination were performed in the remaining 64 pregnant women at gestation weeks 24–28, and for those with a normal result then (n = 48) at gestation weeks 32–34. Glycated haemoglobin (HbA_{1c}) levels were also determined on the fasting blood samples. HbA_{1c} was assayed by microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA), with an interassay CV of 6.4% and an intra-assay CV of 4.4% and reference range < 6.0%. The incidences of the following risk factors for GDM were analysed: any family history of Type 2 diabetes, a history of a large neonate (≥ 4000 g), a history of an adverse perinatal outcome (missed abortion, malformation, polyhydramnios, stillbirth or preterm delivery), obesity {prepregnant BMI [weight (kg)/height^2 (m^2)] ≥ 30}, age ≥ 35 years and glycosuria.

The maternal BMI was calculated and analysed by means of the WHO/NIH classification of overweight and obesity [8–10]. The prepregnant weight or that recorded at the first antenatal visit was used for calculation of the maternal BMI.

Statistical analysis was by ANOVA and multiple logistic regression methods using the Stata Software Package (StataCorp LP, College Station, TX, USA). Hosmer–Lemeshow goodness-of-fit test was performed to check models. The sensitivity, specificity, and positive and negative predictive values of the fasting and post-load insulin level in predicting GDM at gestation weeks 24–28 and 32–34 were calculated. All data are presented as the mean ± SD. Statistical significance was set at the 95% level (P < 0.05).

Results

GDM was diagnosed in 43 (60.5%) of the 71 pregnant women with one or more risk factors for GDM who were referred to our department at gestation week ≤ 16: in seven (16.3%) at the first OGTT before gestation week 16, in 13 (30.2%) at gestation weeks 24–28, and in 23 (53.5%) at gestation weeks 32–34. Seven women had GDM by week 16, 20 by weeks 24–28 and 43 by gestation weeks 32–34. The pregnant women were divided into subgroups on the basis of the gestational age at the onset of GDM (Table 1). The HbA_{1c}, plasma glucose and insulin levels both at fasting and at 120 min decreased with increase in gestational age at the diagnosis of GDM.

The incidence of subsequent GDM was analysed in pregnant women with a negative result (n = 64) on the first OGTT at gestation week ≤ 16. The pregnant women were divided into three subgroups on the basis of the fasting and 120-min serum insulin levels at gestation week ≤ 16: normal at both fasting and 120 min, normal at fasting but increased at 120 min, and both increased (Table 2). No woman had increased fasting but normal 120-min serum insulin levels. In the subgroup of 13 women with increased serum insulin levels both at fasting and at 120 min, GDM occurred in nine at gestation weeks 24–28, and only one did not develop GDM during the pregnancy. In the 18 women with normal fasting and increased 120-min

Table 1 Demographic, morphometric and metabolic parameters at gestation week < 16 of pregnant women grouped on the basis of the time of onset of gestational diabetes mellitus (GDM)

	Onset of GDM			
	At gw ≤ 16	At gw 24–28	At gw 32–34	Non-GDM
No. of cases	7	13	23	28
Age (years)	27.3 ± 5.1	29.8 ± 5.3	29.0 ± 6.0	28.9 ± 5.8
Body mass index (kg/m^2)	27.1 ± 6.6	32.0 ± 7.5*	29.5 ± 6.4	28.2 ± 5.3
Gestational age at first investigation (weeks)	12.0 ± 3.3	13.0 ± 2.0	13.4 ± 2.0	13.1 ± 2.3
HbA_{1c} (%)	7.7 ± 2.2***†‡‡	6.2 ± 0.9	6.0 ± 0.5	5.7 ± 0.5
Plasma glucose (mmol/l)				
Fasting	5.8 ± 1.7***†	5.4 ± 0.7***	4.9 ± 0.5	4.6 ± 0.4
120 min	8.8 ± 1.2***†††‡‡	7.1 ± 0.4***	6.2 ± 1.2	5.6 ± 1.0
Serum insulin (mU/l)				
Fasting	31.8 ± 9.0***††	32.2 ± 6.6***†††	21.5 ± 8.0	16.1 ± 6.3
120 min	96.5 ± 11.6***†	94.7 ± 22.7***††	69.0 ± 24.0**	47.4 ± 22.4
Treatment of GDM				
Diet only	3	9	23	
Diet and insulin	4	4	0	
No. of cases with risk factor				
1 risk factor	4	7	14	19
≥ 2 risk factors	3	6	9	9

gw, gestational weeks.
Significance levels were calculated using Bonferoni method.
Difference from the non-GDM group: *P < 0.05; **P < 0.01; ***P < 0.001.
Difference from the group with GDM at gw 32–34: †P < 0.05; ††P < 0.01; †††P < 0.001.
Difference from the group with GDM at gw 24–28: ‡P < 0.05; ‡‡P < 0.01; ‡‡‡P < 0.001.

Table 2 Age, body mass index, HbA1c, and glucose levels of pregnant women divided into subgroups on the basis of serum insulin level at gestational weeks ≤ 16

	Serum insulin level (mU/l) at gw ≤ 16		
	≥ 30 fasting ≥ 70 120 min	< 30 fasting ≥ 70 120 min	< 30 fasting < 70 120 min
No. of cases	13	18	33
GDM at gw 24–28	9	3	1
GDM at gw 32–34	3	12	8
Non-GDM cases	1	3	24
Age (years)	30.0 ± 5.2	29.2 ± 5.6	28.8 ± 6.1
Body mass index (kg/m^2)	32.4 ± 7.3*	30.2 ± 6.5	27.9 ± 5.3
Glucose (mmol/l)			
Fasting	5.2 ± 0.8*	5.0 ± 0.6	4.7 ± 0.4
120 min	6.8 ± 0.8**	6.6 ± 1.0**	5.6 ± 1.1
HbA_{1c} (%)	6.1 ± 1.0	6.0 ± 0.4	5.9 ± 0.6
No. of cases with risk factor			
1 risk factor	6 (46.2%)	10 (55.6%)	24 (72.7%)
≥ 2 risk factors	7 (53.8%)	8 (44.4%)	9 (27.3%)

gw, gestational weeks; GDM, gestational diabetes mellitus.
Significance levels were calculated using Bonferoni method.
Difference from the group with serum insulin level < 30 mU/l and < 70 mU/l at fasting and at 120 min, respectively, at gw ≤ 16: *P < 0.05; **P < 0.01; ***P < 0.001.

Table 3 Sensitivity, specificity, and positive and negative predictive values of serum insulin levels fasting and at 120 min before gestational weeks 16 for prediction of a glucose intolerance by gestational weeks 24–28 and 32–34

	Increased serum insulin level at gw ≤ 16			
	At fasting (≥ 30 mU/l)		At 120 min (≥ 70 mU/l)	
	GDM by the gestational weeks			
	24–28	32–34	24–28	32–34
Sensitivity, %	69.2	33.3	92.3	75.0
Specificity, %	96.4	96.4	85.7	85.7
Positive predictive value	0.9	0.92	0.75	0.87
Negative predictive value	0.87	0.53	0.96	0.73

gw, gestational weeks; GDM, gestational diabetes mellitus.

serum insulin levels, GDM was present at gestation weeks 24–28 in only three but was present in 12 women at gestation weeks 32–34. Of the 33 cases with normal fasting and 120-min serum insulin levels, 24 did not develop GDM. GDM was apparent in one of these 33 cases at gestation weeks 24–28, and in eight cases at gestation weeks 32–34.

The sensitivity, specificity, and positive and negative predictive values of increased fasting or 120-min serum insulin levels for the prediction of glucose intolerance by gestation weeks 24–28 and 32–34 are shown in Table 3. Increased fasting serum insulin level had the higher positive predictive value compared with increased 120-min insulin level for both gestation weeks 24–28 and 32–34. Higher negative predictive values for both gestation weeks 24–28 and 32–34 were found when the serum insulin level at 120 min was increased rather than the fasting value.

The sensitivity, specificity, and positive and negative predictive values of increased fasting serum insulin levels for the prediction of impaired fasting glucose (IFG) by gestation weeks 24–28 and 32–34 were also calculated. Increased fasting serum insulin (> 30 mU/l) predicted IFG at gestation weeks 24–28 with a sensitivity of 94%, specificity of 50%, positive predictive value 0.37 and negative predictive value 0.96. Increased fasting serum insulin (> 30 mU/l) predicted IFG at gestation weeks 32–34 with a sensitivity of 76%, specificity of 87%, positive predictive value 0.65 and negative predictive value 0.92.

The prevalence of risk factors for GDM were as follows: family history of diabetes 49.3% (35 out of 71); obesity (prepregnant BMI ≥ 30 kg/m^2) 46.5% (33 out of 71); age ≥ 35 years 21.1% (15 out of 71); glycosuria 15.5% (11 out of 71); history of large neonate (≥ 4000 g) 9.9% (seven out of 71); history of adverse perinatal outcome (included missed abortion, malformation, stillbirth) 5.6% (four out of 71). Twenty-seven of the 71 women had more than one risk factor for GDM.

Univariate analysis showed that fasting and 120-min plasma glucose, HbA_{1c}, BMI, fasting insulin with a range of odds ratios (OR) of 1.4–31.0 and wide confidence intervals (CI) significantly predicted GDM at 24–28 and 32–34 weeks, except for BMI for GDM at gestation weeks 32–34. Plasma glucose levels and serum insulin levels at fasting and at 120 min, HbA_{1c} and BMI were used in the multiple logistic regression analysis. Increased serum insulin level at fasting (OR 16.6, 95% CI 2.06, 134.2) was the best predictor of GDM at gestation weeks 24–28 in the multiple logistic regression model. In addition, increased serum insulin level at 120 min (OR 13.3, 95% CI 3.07, 57.9) was the best predictor of GDM by gestation weeks 32–34. There was no relationship between raised HbA_{1c} and GDM at either gestation weeks 24–28 (OR 4.3, 95% CI 0.67, 27.8) or weeks 32–34 (OR 1.6, 95% CI 0.44, 5.53). BMI, plasma glucose level at fasting and 120 min did not enter the multiple regression model. All models had a good fit.

Discussion

GDM has been characterized as the onset or recognition of glucose intolerance during the current pregnancy [11]. GDM is a heterogeneous entity which includes both pregnancy-induced glucose intolerance and undiagnosed alteration of the carbohydrate metabolism discovered during pregnancy. The increase in the insulin level starts at gestation weeks 16–18 [12]. Hyperinsulinaemia after this gestational age reflects an approximately two- to three-fold increase in the insulin level, induced by pregnancy. Hyperinsulinaemia before this gestational age demonstrates that the patient is really hyperinsulinaemic, independent of the pregnancy.

Hyperinsulinaemia is a significant risk factor for diabetes mellitus. We consider hyperinsulinaemia in the non-pregnant state or before gestation weeks 16–18 to be a risk factor for GDM, as it implies insulin resistance. We hypothesized that hyperinsulinaemia in a pregnant woman merely requires time to transform to GDM.

Until now only a few studies have used the insulin level to predict insulin resistance or GDM. Several authors have examined the insulin level during and after pregnancy in patients with GDM in order to predict the development of diabetes mellitus [13,14]. However, we have found no prospective evaluation of the fasting insulin level or the insulin response to a 75-g OGTT in early pregnancy to predict later GDM during the index pregnancy.

Ergin *et al*. examined the insulin response to a 100-g 3-h OGTT in 120 Turkish women between 24 and 28 weeks' gestation [15]. The fasting insulin level and insulin resistance were similar in patients with a single abnormal value during the OGTT and those with GDM.

Kirwan *et al*. investigated insulin sensitivity indicated by an OGTT and also fasting glucose/insulin levels in an effort to predict insulin sensitivity in women before and during pregnancy [16]. They repeated a 2-h euglycaemic-hyperinsulinaemic clamp and a 120-min OGTT (a 75-g load in prepregnancy, and a 100-g load in pregnancy) in 15 women in prepregnancy and in both early (12–14 weeks) and late (34–36 weeks) pregnancy. They found that the insulin sensitivity indicated by the OGTT is a better indicator of insulin sensitivity than the fasting glucose and insulin values. However, the use of such an inconvenient method clearly limits the numbers that can be studied.

Clark *et al*. found that patients with GDM had higher insulin and C-peptide levels both at fasting and at 2 h compared with non-GDM patients [17]. They determined insulin and C-peptide between 16 and 33 weeks' gestation, and found that these variables were predictive of GDM individually. They suggested that GDM should be looked upon as a component of the syndrome of insulin resistance.

Swinn *et al*. concluded that the excessive secretion of insulin precursors characterizes and predicts GDM [18]. They examined the insulin, the intact proinsulin and the 32,33-split proinsulin response to an OGTT in 64 women with GDM and in 154 non-GDM control subjects of comparable age and BMI. The women with GDM were characterized by higher plasma insulin and intact proinsulin levels at 120 min and by elevated 32,33-split proinsulin levels both at fasting and at 120 min. These insulin secretion abnormalities in GDM patients are similar to those seen in non-pregnant subjects with impaired glucose tolerance. They also measured insulin and proinsulin-like molecules in women with a 1-h glucose level of > 7.7 mmol/l after a 50-g glucose challenge at 28–32 weeks of gestation. The percentage of total insulin-like molecules accounted for by proinsulin-like molecules was significantly elevated in those women in whom a subsequent OGTT showed GDM compared with those in whom the later OGTT was normal. To improve the predictive power of screening tests for GDM, Swinn *et al*. suggested the incorporation of a measurement of the percentage of proinsulin-like molecules in the routine 50-g screening test. In our view, the incorporation of serum insulin determinations at fasting and at 120 min in the screening protocol for GDM seems worthwhile and more applicable than the calculation of proportions of proinsulin, or the use of expensive and inconvenient methods. However, this is applicable only in pregnant women with a risk factor for GDM before 16 weeks' gestation.

We found a positive correlation between serum insulin level and the subsequent manifestation of GDM. The higher the serum insulin level, the earlier the manifestation of GDM. Most (83.3%) of the pregnant women with an elevated serum insulin level at 120 min subsequently developed GDM by gestation weeks 32–34. GDM was present at gestation weeks 24–28 in 69.2% of those with elevated serum insulin levels both at fasting and at 120 min, and at gestation weeks 32–34 in 66.7% of those with a normal fasting level but an increased 120-min serum insulin level at ≤ 16 gestation week. However, GDM did not develop at all in 72.7% of those with normal serum insulin levels both at fasting and at 120 min at ≤ 16 gestation week.

Increased serum insulin levels both at fasting and 120 min before gestation week 16 were strongly predictive of the development of GDM by gestation weeks 32–34 with an OR of 16.6 and 13.3, respectively.

As a fasting plasma glucose level of 5.6 mmol/l is the generally accepted cut-off value for IFG, we analysed fasting serum insulin levels in order to predict the subsequent development of IFG [19]. We found that increased fasting serum insulin level (> 30 mU/l) at gestation week ≤ 16 has very good sensitivity (94%) and poor specificity (50%) to predict IFG at gestation weeks 24–28. The sensitivity decreased to 76% but the specificity increased to 87% for the development of IFG at gestation weeks 32–34. Negative predictive values were very high at both gestation weeks 24–28 and 32–34. However, IFG is not a diagnostic criterion for GDM, so pregnant women with IFG should undergo a subsequent OGTT.

Measurement of fasting and 2-h insulin during an OGTT before gestation week 16 might reduce the number of subsequent screening tests for GDM, in addition to facilitating optimal timing of the subsequent screening procedures. Furthermore, earlier introduction of the appropriate management of the pregnant women may prevent some complications of GDM, such as increased fetal growth.

Conclusions

Fasting and 2-h serum insulin measurements at ≤ 16 gestation week is an easy and reliable method with which to predict GDM in patients with a risk factor for GDM. Because of the very high positive predictive value of the method for GDM at gestation weeks 32–34, pregnant women with an elevated fasting and/or 120-min serum insulin level at ≤ 16 gestation week should be managed in the same way as those with a diagnosis of glucose intolerance, in spite of normal blood glucose values during the OGTT. Given the very high negative predictive value of the method at gestation weeks 24–28, pregnant women with normal serum insulin levels at fasting and at 120 min at ≤ 16 gestation week should undergo a subsequent OGTT only at gestation weeks 32–34. Because obesity is one the most frequent risk factors for GDM, a calorie-restricted diet might be considered for a pregnant women with obesity, independently of the results of the OGTT.

Competing interests

None declared.

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