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RESEARCH

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First trimester 75g oral glucose tolerance test (oGTT) in a population at high risk for gestational diabetes

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Abstract

Introduction: *In women at high-risk for gestational diabetes (GDM), it is recommended to exclude pre-gestational diabetes (PGDM) by measuring a random or fasting glucose, or glycosylated haemoglobin (HbA1c), or by a 75g oral glucose tolerance test (oGTT) in the first trimester. In this study, we evaluated whether this first trimester 75g oGTT is also useful in stratifying pregnant women at high risk for GDM.*

Methods: *At the first antenatal visit pregnant women at high risk for PGDM were screened using a 75g oGTT. If PGDM was excluded, a second 75g oGTT was performed between 24 and 28 weeks of gestation, in accordance with the HAPO-trial. Mann Whitney U test, Chi^2 test, and ROC analysis were used for statistical purposes.*

Results: *131 women were included. First trimester oGTT glucose values were higher in women who later developed GDM (fasting 4.93±0.72 vs. 4.23±0.47; 1h: 7.48±1.8 vs. 6.84±1.26; 2h: 7.60±1.57 vs. 5.66±1). The cut-off value, derived from the ROC analysis used to calculate the diagnostic indices, was 4.35mmol/L, 7.25mmol/L, and 6.25mmol/L for fasting, 1h, and 2h glucose values, respectively.*

Conclusions: *A first trimester 75g oGTT to exclude PGDM may be also useful in discriminating those who will develop GDM in the third trimester.*

Keywords: *first trimester; oral glucose tolerance test (oGTT); gestational diabetes (GDM)*

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance, which is first detected during pregnancy [1]. It is a common condition with an incidence of 9.3% to 25.5% in the IADPSG collaborating centres using the HAPO diagnostic criteria [2] and the incidence is rising constantly [3]. Besides increasing maternal age this development is explained with the pandemic increase of overweight persons [4]. Similarly, the prevalence of prediabetes compromising of impaired fasting glucose (IGF) and impaired glucose tolerance (IGT) and diabetes type 2 is increasing steadily [5]. Since decades, GDM is a well-known metabolic disorder, which, left undiagnosed or untreated, affects negatively the course of the pregnancy. Indeed, a higher rate of fetal and maternal complications is expected which in turn will sensibly affect the already high caesarean section rate [6,7]. The HAPO-trial was able to find a linear association between the level of blood glucose and adverse pregnancy outcome [7]. Therefore, treating maternal hyperglycaemia is imperative and randomized trials have shown a significant benefit on doing so [1,8]. Many national and international societies have introduced or proposed a general screening for pre-existing diabetes (PGDM) in the first trimester or gestational diabetes later on. To date it is recommended to exclude PGDM in a high-risk population by measuring either a random or fasting glucose or HbA1c in the first trimester. Also a 75g oGTT is a proposed option to diagnose or exclude PGDM in the first trimester. Of note, the diagnostic criteria at this gestational age are those proposed for the non-pregnant population [1].

In the current study, the aim was to evaluate whether a 75g oGTT performed during the first trimester in a group of pregnant women at high-risk for GDM might be also useful in screening for GDM.

Methods

During a period of 40 month (from September 2007 to December 2010) we screened pregnant women at high risk for PGDM by using a 75-g oGTT scheduled for their first prenatal visit at our department. Venous blood samples were collected at 0, 1 and 2h after the glucose load.

Pregnant women were classified as at risk for PGDM when at least one of the following criteria was fulfilled: obesity (BMI≥30kg/m^2), first-degree relative with diabetes, women with

polycystic ovarian syndrome (PCO syndrome), high-risk ethnicity (African or Asian), GDM or history of a macrosomic (>4000g) or malformed neonate in a previous pregnancy. Moreover, women who suffered a past late miscarriage (>20 weeks gestation) were also screened. All high-risk women in whom a PGDM (fasten plasma glucose (FPG) ≥7mmol/l or 2-h plasma glucose (PG) ≥11.1mmol/l) or prediabetes (impaired fasting glucose [IFG] of 5.6-6.9mmol/l, and/or impaired glucose tolerance [IGT] with a 2 hour glucose of 7.8-11.0mmol/l) has been excluded in the first trimester underwent a second 75-g oGTT between 24 and 28 weeks of gestation as part of our general screening strategy to exclude GDM. Before 2008, we used the ADA [8] and/or WHO [9] criteria to define GDM. This strategy was changed thereafter and now we are using the diagnostic criteria proposed by our society [10] and by the American Diabetes Association [1], which are based on the results of the HAPO trial (FPG ≥5.1mmol/L, 1-h PG ≥10mmol/L and a 2-h PG ≥8.5mmol/L) [7]. To uniformly analyse our data we retrospectively adopted the latter criteria for the whole population included in this trial. No women underwent treatment before GDM was diagnosed on the basis of the second oGTT. The study was approved by the local ethics committee (KEK Bern).

Statistical analysis was performed with GraphPad Prism 5.0 for Mac OSX. Continuous variables were compared using the paired student t-test or the Mann-Whitney U-test. Proportions were analysed utilizing the Fisher exact test. Correlations were searched using the Spearman rank correlation test. Receiver operating characteristic (ROC) curves were constructed to describe the relationship between sensitivity and false-positive rate of first trimester fasting, 1-h, and 2-h plasma glucose values in predicting GDM between 24 and 28 weeks of gestation. A p values of <0.05 was considered significant.

Results

In this study 135 pregnant women at risk for GDM, were included. No case of PGDM was diagnosed and 4 cases with prediabetes were excluded from further analysis. The clinical characteristics of our study population are presented in table 1 dichotomized between women with and without GDM. Gestational age at inclusion respectively at first trimester oGTT was 11.9±0.24 weeks (median 12.3, range 9.4-13.0) of gestation. The caesarean section rate was 54/135 (40%) and 6/135 (4%) pregnancies were complicated by hypertensive disorders.

The prevalence of GDM in our study population was 17/131 (13%). Table 2 summarizes the first trimester oGTT plasma glucose values at 0, 1, and 2 hours measured in our cohort of women subdivided in those which fulfilled the diagnostic criteria for GDM in the third trimester, and those who did not. Pregnant women who were diagnosed to have GDM had significantly higher first trimester oGTT plasma glucose values at each time point. The cut-off value, derived from the ROC analysis used to calculate the diagnostic indices, was 4.35mmol/L (LHR 1.96; sensitivity 82.4%, specificity 57.9%), 7.25mmol/L (LHR 2.04; sensitivity 82.4%, and specificity 59.7%), and 6.25mmol/L (LHR 2.54; sensitivity 82.4%, specificity 67.5%) for fasting, 1h, and 2h glucose values, respectively (Table 3, Graphic 1 to 3).

Comparing the first trimester 75g oGTT plasma glucose values with those obtained in the third trimester, the fasten glucose values (4.23±0.47 vs. 4.05±0.44; p=0.0005), and the one hours values (6.84±1.26 vs. 7.16±1.41; p=0.03) were significantly different in the group without GDM. No difference was found comparing the two hours plasma glucose values (5.66±1.01 vs. 5.71±1.03; p=0.69). A moderate correlation was found between all first and third trimester oGTT results (fasten: r=0.34; p=0.0002; 1h: r=0.31; p=0.0007; 2h: r=0.35; p=0.0002). In the GDM group all oGTT values were different comparing the first and third trimester results (fasten: 4.93±0.72 vs. 4.58±0.41 p=0.01; 1h: 9.48±1.8 vs. 8.34±1.26; p=0.005; 2h: 7.6±1.57 vs. 6.69±0.55; p=0.03). In contrast to the non GDM group, all third trimester values were lower than the first trimester oGTT results, and a correlation was found only between the fasten (r=0.49; p=0.048), and the 1 hours values (r=0.65; p=0.0052).

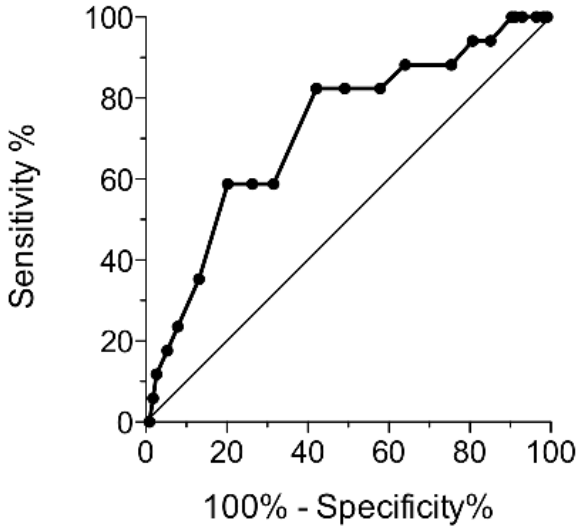

Figure 1. First trimester receiver-operator characteristics (ROC) curve analysis for fasting hour plasma glucose values

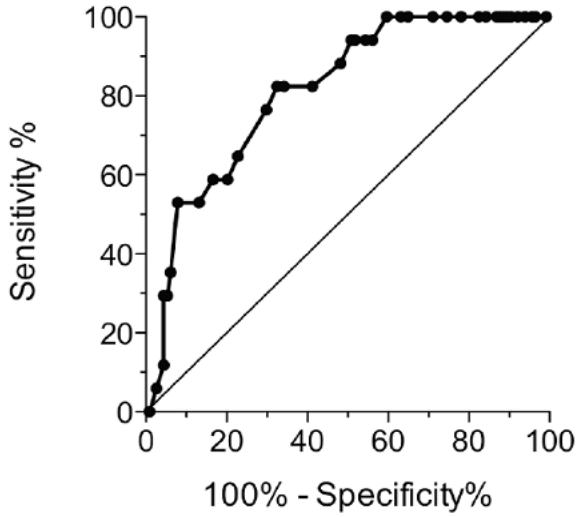

Figure 2. First trimester receiver-operator characteristics (ROC) curve analysis for one hour plasma glucose values

Characteristics	GDM group (n=17)	Non GDM (n=114)	Significance
Age (years±SD)	31.5±5	29.8±5.5	NS
BMI (kg/m^2)	27.3±3.7	25±5.1	<0.05
Nulliparity (n, %)	5 (29.4%)	51 (44.7%)	NS
Gestational age at delivery (weeks±SD)	38.8±1.8	39.3±1.9	NS
5' Apgar score (mean±SD)	8.8±1.1	8.9±1.1	NS

Table 1: Clinical characteristics of the study population dichotomized between pregnant women with and without gestational diabetes

oGTT plasma glucose values (mmol/l)	GDM (n=17)	no GDM (n=114)	Significance
fasten	4.93±0.72	4.23±0.47	p=0.0003
1 hours	9.48±1.8	6.84±1.26	p=0.0017
2 hours	7.6±1.57	5.66±1.01	p=0.0011

Table 2. First trimester 75g oGTT plasma glucose values of pregnant women with and without diagnosis of GDM in the third trimester

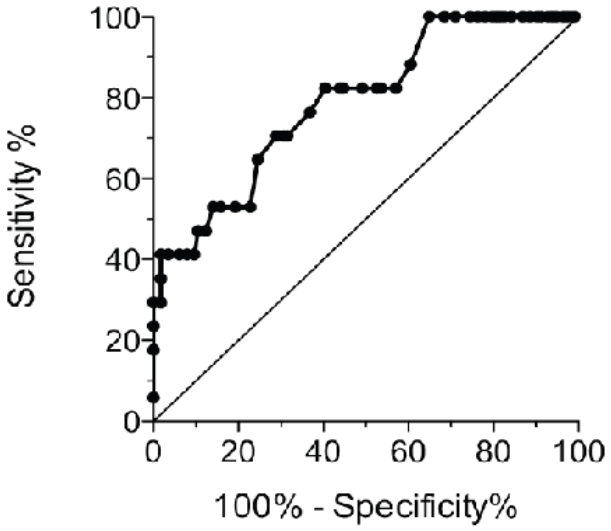

Figure 3. First trimester receiver-operator characteristics (ROC) curve analysis for two hour plasma glucose values

oGTT plasma glucose values (mmol/l)	Cut-off (mmol/l)	LHR	Sensitivity	Specificity	AUC (95%CI), significance
fasten	>4.35	1.96	82.4%	57.9%	0.72 (0.59-0.85); p=0.04
1 hour	>7.25	2.04	82.4%	59.7%	0.79 (0.68-0.90), p=0.0001
2 hours	>6.25	2.54	82.4%	67.5%	0.81 (0.72-0.91); p<0.0001

LHR: Likely Hood Ratio; AUC: Area Under the Curve

Table 3. First trimester 75g oGTT plasma glucose cut-off's derived from receiver-operator characteristics (ROC) analysis in predicting GDM

Discussion

This study shows that in a high-risk population all first-trimester oGTT values are already increased in women who later develop GDM compared to those who had a normal oGTT at 24-28 weeks. While it is an accepted policy recommended by the American Diabetes Association (ADA) [1] to perform either a glycosylated haemoglobin (cut-off value ≥ 6.5%) and/or a fasting blood glucose (cut-off value ≥7 mmol/L), or a 75g OGTT to rule out PGDM, there is only limited information so far on the use of an early oGTT in screening for GDM. Recently others and we could demonstrate that HbA1c levels between 5.7% and 6.4% in the first trimester can be considered a risk factor for the development of GDM [11,12]. Our findings of an altered oGTT in the first trimester adds another factor, which shows that metabolic changes are already present in the first trimester in women who later develop GDM and that screening for GDM in the first trimester is feasible.

Even though we only included women at high risk, the prevalence of GDM in this study was only 13%. This is similar to the prevalence we found in our two recently published studies in a general population [12,13]. We explain this by the fact that we defined certain ethnical origins alone as well as malformation and late miscarriage in a previous pregnancy also as risk factors and included them to our collective. However the prevalence of GDM of 14-15% in our recent studies is in line with the prevalence's mentioned by the ADA of 15-20% [1]. In the general population we found that women developing GDM were significantly older, had a higher BMI and were significantly less often primiparous. In this study the average maternal age was lower than in the previously published, probably reflecting the increasing maternal age over time, as the data in the previous study is more recent. The BMI in this study is higher in the non-GDM group, nulliparity is similar in both studies. So on average the two

populations are very comparable, which also explains the similar incidence in GDM.

As mentioned previously, the ADA recommends amongst other possibilities to perform a 75 oGTT to rule out overt diabetes in the first trimester. Plasencia et al. also compared early (6-14 weeks) to late (20-30 weeks) oGTTs. However, instead of the 75 oGTT they used a 50g glucose challenge test followed by a 100g oGTT when the postprandial value was >7.8mmol/l in the challenge test [14]. Due to different criteria of diagnosing GDM, not in line with the HAPO criteria, they had a much lower incidence of GDM in their collective. However, in accordance to our results, they could demonstrate higher postprandial levels already in the first-trimester in women who later develop GDM. They also performed ROC-analyses to define the ideal cut-off using the 50g challenge test result. Our study is, to our knowledge, the first to define which cut-offs distinguish best for third trimester GDM using the plasma glucose values derived from a 75g oGTT.

Interestingly we found that the plasma glucose values at the third trimester oGTT were significantly lower compared to those found in the first trimester only in the GDM group but not in the non-GDM group. Insulin resistance increases throughout pregnancy and insulin response is reduced in GDM compared to pregnancies without GDM [15]. So the finding of lower glucose values at 24 to 28 weeks compared to 12 weeks in the GDM group is surprising. Catalano et al studied insulin sensitivity between 12 and 34 weeks gestation and noted a decrease of 50-60% in both GDM and uneventful pregnancies [15]. However in healthy pregnancies higher insulin levels compensate for this reduced tissue response. Siegmunds et al. used continuous glucose monitoring system in healthy pregnancies to study the course of glucose levels and only at 36 weeks an increase in mean glucose values was noted [16]. In their study they also examined changes in oGTT values between 16 and 36 weeks of gestation and found no significant difference in any values [16]. According to Catalano, obese women peak with the insulin level after meals at different times than lean women. He also found that the change in insulin-sensitivity in the first trimester is dependant on the changes in adipose tissue. Indeed, women with a GDM had a higher BMI than those that did not develop GDM in this study. Even though not completely explained, the higher prevalence of obese women in our GDM-group might explain in part these findings.

Screening for GDM in the first trimester remains a challenge. As others and we could show, fasting and postprandial plasma glucose values are already increased in the first trimester in women who later develop GDM. We could confirm the findings already noted in a low risk population, that fasting plasma glucose is not a very good predictor of GDM [17, 18], the postprandial levels are significantly different however. The value of screening already in the first trimester using a 75g oGTT remains debatable. The experience shows that using glycosylated haemoglobin is easier and better accepted by patients than performing an oGTT [11,12]. Moreover, our results underline again the problem, that cut-offs used to define prediabetes or diabetes in a non-pregnant population are not always applicable to pregnant women. The ROC curve analysis show that the 2h value of >6.25mmol/l yield the best performance in predicting the occurrence of GDM in the third trimester.

From a more theoretical point of view interventions based on life style adjustments, diet and/or medications (insulin or metformin) starting already in the first trimester might have the potential to further reduce adverse pregnancy outcome and birth complications than screening and start treatment in the third trimester [19]. However, appropriate studies investigating this issue are still missing..

Conclusions

Today there is convincing evidence, that screening for GDM in the first trimester is feasible best by measuring glycosylated haemoglobin. However, when using a 75g oGTT in the first trimester to rule out PGDM or prediabetes in a group of pregnant women at high risk, the plasma glucose values and in particular the 2-h value might be also indicative for a disturbed metabolic state such as GDM.

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