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The impact of gestational diabetes mellitus on pregnancy outcome comparing different cut-off criteria for abnormal glucose tolerance

Running headline: Pregnancy outcome and gestational diabetes

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Abstract

Objective. To examine pregnancy outcomes in relation to different categories of glucose tolerance during pregnancy.

Design. Prospective observational cohort study.

Setting. Patient recruitment and data collection were performed in four delivery departments in southern Sweden.

Population. Women delivering during 2003-2005; 306 with gestational diabetes mellitus, 744 with gestational impaired glucose tolerance, and 329 randomly selected controls.

Methods. All women were offered a 75 g oral glucose tolerance test during pregnancy. On the basis of their capillary 2-hour plasma glucose concentrations three groups were identified; gestational diabetes mellitus ($\geq$10.0 mmol/l), gestational impaired glucose tolerance (8.6-9.9 mmol/l), and controls (<8.6 mmol/l). Data for the groups were compared using a population-based database.

Main outcome measures. Maternal and fetal outcomes.

Results. For the gestational diabetes mellitus group adjusted odds ratios (95% confidence intervals) for hypertensive disorders during pregnancy, induction of labor and emergency caesarean section were 2.7 (1.3-5.8), 3.1 (1.8-5.2), 2.5 (1.5-4.4) respectively; and for Apgar score <7 at 5 min, need for neonatal intensive care >1 day and large-for-gestational age infant 9.6 (1.2-78.0), 5.2 (2.8-9.6), 2.5 (1.3-5.1) respectively. The increases in odds ratios for the gestational impaired glucose tolerance group were less pronounced but still significant for hypertension during pregnancy, induction of labor, large-for-gestational age infant and use of neonatal intensive care >1 day, with odds ratios (95% confidence interval) 2.0 (1.0-4.1), 1.8 (1.1-3.0), 2.1 (1.1-3.9), 2.1 (1.1-3.8) respectively.

Conclusions. These data indicate that even limited degrees of maternal hyperglycemia may affect the outcome of pregnancy.

Key words: OGTT, gestational diabetes mellitus, impaired glucose tolerance, pregnancy outcome

Abbreviations

CI   Confidence interval

GDM   Gestational diabetes mellitus

IGT   Impaired glucose tolerance

OGTT   Oral glucose tolerance test

OR   Odds ratio

PRS   Perinatal revision south

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (1). Although it is well recognized that GDM is a marker of subsequent diabetes (2, 3), screening and treatment of mild GDM has been questioned due to the lack of convincing data regarding possibility to improve the outcome (4, 5) and up to now there has been only a few randomized trials demonstrating a beneficial effect of treatment (6, 7).

Outside the United States, the most widely used criteria for the diagnosis of GDM are those recommended by the World Health Organization (WHO) for diabetes mellitus in non-pregnant adults, which are based on a 75 g oral glucose tolerance test (OGTT) (8). In 1991, the Diabetes Pregnancy Study Group of the European Association for the Study of Diabetes suggested a 2-hour capillary blood glucose concentration of ≥ 9 mmol/l, corresponding to the 95th percentile, to be the diagnostic criterion for GDM (9). With some exceptions, this recommendation has been followed in Sweden.

In 1999, the WHO criteria were revised and GDM was redefined to include the categories of diabetes and impaired glucose tolerance (IGT) in non-pregnant adults (10). In the light of these new criteria a prospective study was designed. In the years 2003-2005 pregnant women in southern Sweden representing different glucose categories according to the OGTT were invited to take part in a 5-year follow-up program. The aim of the present study was to evaluate differences in pregnancy outcome in relation to the OGTT results during pregnancy for the participating women.

Material and methods

In 1995 a general screening program for GDM was introduced in southern Sweden offering an OGTT at the local antenatal clinic to all women in week 28 of their pregnancy, and also in week 12 if they had a first-degree family history of diabetes or GDM in previous pregnancies. A 2-hour capillary blood glucose concentration of ≥ 9.0 mmol/l was regarded as diagnostic for GDM. If glucose concentrations were between 7.8 and 8.9 mmol/l, implying gestational impaired glucose tolerance (gestational IGT), the OGTT was repeated within one week. The laboratory procedure using HemoCue devices (HemoCue, Ängelholm, Sweden) has shown a coefficient of variation of 3.1-3.7% (11).

Women diagnosed with GDM were transferred to specialist antenatal care and had regular contact with a diabetologist. They were given advice on diet as well as physical activity, and were closely monitored by self-tests of blood glucose, six times daily if receiving insulin treatment, and six times every other day if not. Glucose values repeatedly ≥ 6 mmol/l before meals or ≥ 8 mmol/l one hour after meals were indications for insulin treatment. Intensified fetal supervision involved more frequent midwife and doctor controls, extended ultrasound examinations, and cardiotocography. Women diagnosed with gestational IGT were given advice on diet and physical activity, but followed the routine pregnancy program and did not perform blood glucose tests, unless a repeat test was diagnostic for GDM.

Women who were delivered during 2003-2005 were invited to take part in the present study, covering 86% of all pregnancies in the County of Skåne in southern Sweden, including four of five delivery departments. During the recruitment period there were 32 716 deliveries in the participating hospitals and the estimated number of women with GDM and gestational IGT were 407 and 1 193 respectively. All women who accepted the invitation to participate provided written informed consent. The results from their OGTTs were identified and the use of correct sampling technique was ensured (11). Since routine glucose measurements in Sweden switched from blood to plasma glucose measurements during the second year of the study period, cut-off values for plasma glucose were established. A HemoCue glucose meter was introduced, converting blood glucose concentrations to equivalent plasma glucose concentrations by multiplying by a constant factor of 1.11 (12). A control group was formed by selecting every 24th woman from each participating hospital, from the consent forms, with a 2-hour blood glucose value of <7.8 mmol/l (plasma glucose <8.6 mmol/l), implying

gestational normal glucose tolerance, n = 352. All women with 2-hoour blood glucose values of 7.8-8.9 mmol/l (plasma glucose 8.6-9.9 mmol/l) at the initial OGTT, comprised the gestational IGT group, n = 812. The GDM group consisted of women with 2-hour blood glucose ≥9.0 mmol/l (plasma glucose ≥10.0 mmol/l), n = 342.

In order to describe pregnancy outcomes for the groups, clinical data from the population-based perinatal database, Perinatal Revision South (PRS), were used. The PRS started in 1995, is based on approximately 18,000 annual births and is compiled from data reported from all nine obstetric units and all seven neonatal units in the southern region of Sweden (13). Information was available in the PRS for a total of 1379 women; 306 GDM, 744 gestational IGT, and 329 controls. Data for the GDM and gestational IGT groups were tested against the controls.

The following outcomes were studied: frequency of hypertension, including preeclampsia (defined as diastolic blood pressure greater than 90 mm Hg on more than one occasion at least 4 h apart, combined with albuminuria of more than 0,3 g/l or 0.3g/24 h on more than one occasion at least 4 h apart), both essential and pregnancy induced hypertension (defined as diastolic blood pressure greater than 90 mm Hg on more than one occasion at least 4 h apart, without significant albuminuria), induction of labor, use of cesarean section, forceps or vacuum extraction, large-for-gestational age infants (defined as birthweight >+2 SD), small-for-gestational age infants (defined as birthweight <-2 SD), infants borne before gestational week 37, Apgar score <7 at 5 min, need for treatment >1 day at the neonatal intensive care unit, rates of perinatal mortality (starting from pregnancy week 22), malformation (classified in accordance with the WHO International Classification of Diseases, 10th revision; dislocation of the hip, preauricular tags, undescended testes and patent ductus arteriosus were not classified as anomalies), Erb's palsy, hyperbiliruminemia (defined as jaundice requiring phototperapy) and neonatal hypoglycemia (defined as a plasma glucose value <2.6 mmol/l).

Odds ratios (OR) and 95 % confidence intervals (CI) for dichotomous outcomes were calculated using multiple logistic regression (Gauss^{TM}, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com). Adjustments were made for maternal age, number of deliveries, and when specified, labor induction and infant birthweight. In order to determine the best multivariate models the following steps were taken: First, the best model for each investigated variable (linear, quadratic, or divided into designed class variables) was

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determined by investigating the level of significance and goodness of fit according to the Hosmer-Lemeshov test. It was revealed that maternal age was most efficiently represented by three class variables (<35 years [reference group], 35-39 years, and 40 years or more). Maternal parity was best expressed as women with one delivery before the index pregnancy vs. more than one delivery. In the models in which induction of labor and infant birth weight were included, induction was included as a binary variable (yes/no), and infant birthweight entered the model using one linear and one quadratic variable. For each model, the number of investigated factors never exceeded 1/10 of the number of cases.

The Kruskal-Wallis test was used to test for differences between group medians. Chi-square tests and Fisher's exact tests were used for comparison of group frequencies.

The study was carried out in accordance with the World Medical Association Declaration of Helsinki (14). Ethical approval was obtained from the Ethics Committee of the Medical Faculty, Lund University, Sweden.

Results

Study group characteristics of participating women and their newborns are shown in Table 1. There were significant inter-group differences in maternal age (p = 0.0155), proportion of women with previous deliveries >1 (p=0.02), and in gestational age (p <0.00001), whereas z-score (SD-units) for birthweight did not differ between groups (p = 0.908).

The results of the risk assessment analysis are shown in Table 2. Compared to controls an increased risk for both GDM and gestational IGT was found with increasing age and the same applied to deliveries (1 vs. >1), although not statistically significant for gestational IGT. All figures are therefore stratified for maternal age and deliveries. Overall the results in women with gestational IGT were intermediate between those of the women with GDM and controls.

GDM as well as gestational IGT were associated with an increased risk of hypertensive disorders during pregnancy and the use of induction of labor was also more common in both groups. There was no elevated number of planed cesarean sections in any of the groups, but for women with GDM the rate of emergency cesarean section was increased. These results remained after adjustment for induction of labor and birthweight (OR 2.5, 95% CI 1.4-4.3).

The frequency of Apgar score <7 at 5 min was increased in infants born to mothers with GDM as was premature deliveries. The estimates for premature deliveries did only marginally change when induced pregnancies were excluded; OR (95% CI) 3.5 (1.6-7.7) for GDM and 2.0 (0.9-4.2) for gestational IGT. Also the rate of large-for-gestational age infants was increased both in women with GDM and gestational IGT, while the rate of small-for-gestational age infants was similar in all groups. Neonatal intensive care was however needed more often in infants born to mothers with GDM as well as gestational IGT.

The number (%) of reported perinatal deaths, malformations and Erb´s palsy in infants born to women with GDM were 3 (0.9), 5 (1.6), 1 (0.3) respectively as compared to 0, 12 (1.6), 2 (0.3) in infants born to women with gestational IGT and 0, 3 (0.3), 0 in infants born to controls. The corresponding figures for reported hyperbilirubinemia were 7 (2.3), 7 (0.9), 2 (0.6) in infants born to women with GDM, gestational IGT and controls respectively; and for hypoglycemia 20 (6.5), 6 (0.8), 0 respectively. The rate of hypoglycemia was significantly increased in infants born to women with GDM compared to controls (p $<10^{-6}$).

Discussion

The present results show that when an OGTT is used as a generalized screening method for abnormal glucose tolerance during pregnancy, also moderately increased glucose levels are associated with an increased risk of pregnancy related complications. This is in line with previous studies (6, 7, 15-20) suggesting a continuum of perinatal risks for women with glucose tolerance within the near-normal range, and has recently been confirmed by the Hyperglycemia and Adverse Pregnancy outcome (HAPO) study, demonstrating a strong continuous association of maternal glucose levels, below those diagnostic of diabetes, with various outcomes (21).

When confronting decisions in connection with pregnancy complications some actions like induction of labor, elective caesarean section, or referral to the neonatal intensive care unit, can be influenced by awareness of the mother's GDM diagnosis. In the present study inductions were used three times as often and referral to neonatal intensive care five times as often in the GDM group as in the controls and the figures were doubled in the gestational IGT group. To some extent these findings may be related to the knowledge of the diagnosis by the attendant physician. However, since women with gestational IGT were regarded as having a normal pregnancy and were not offered intensified fetal supervision, unless diagnosed as GDM on a repeat test, decisions in this group of women do not run the same risk of being biased as in the GDM group.

Increased birthweight as a result of GDM is a consistent finding in most studies and many authors mention an increase in cesarean deliveries as one of the most important complications of GDM (5, 7, 15-17). The rate of elective cesarean section was not increased in any of the groups in the present material. However, in women with GDM the rate of emergency cesarean section was significantly increased as compared to controls. The same came true for the rates of large-for-gestational age infants and Apgar score <7 at 5 minutes, which strengthen the notion that women with GDM actually represent a true high-risk group. Moreover, the increased rate of induction of labor in both groups of women with abnormal glucose tolerance may very well reflect the increased number of women with hypertensive disorders and large-for-gestational age infants in these women.

Several reports support an association between GDM and hypertensive complications during

pregnancy (5, 6, 22-25), which however may be influenced by various confounders, such as age and bodyweight (17, 22, 23). Unfortunately, age and number of deliveries were the only potential confounders possible to control for in the present material, since bodyweight was not reported to the PRS at the time of the study. Furthermore, the material was not large enough to evaluate the individual contributions of preeclampsia, essential or gestational hypertension to the overall increased rate. Aside from the sample size, another limitation of the study is the participation rate, approximately 25% of eligible women with GDM and 40% of women with gestational IGT not being included.

Data on perinatal mortality, malformation, Erb´s palsy, hypoglycemia and hyperbilirubinemia showed a trend towards higher rates with increasing glucose levels but the numbers were small and therefore not included in the risk assessment analysis. These adverse outcomes are probably associated with more severe glucose elevations and therefore require a larger material to prove a difference.

Taken together, our data indicate that even moderately increased glucose levels, within the lower IGT range of the OGTT as defined by the WHO, may affect the outcome of pregnancy. However, the WHO criteria, like those used by others in different parts of the world, are not based on the pregnancy outcome. The HAPO study was designed to address this issue (21) and a group of experts are now developing an international consensus for the diagnosis of carbohydrate intolerance during pregnancy, providing lower thresholds than those currently used all over the world (26).

Acknowledgements

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Table legends

Table 1.

Characteristics of participating women and their newborns

*median (range), †n (%)

The percentage is calculated on all non-missing data for each variable within each group.

Table 2.

Outcomes in mothers and infants

The percentage is calculated on all non-missing data for each variable within each group.

Odds ratios (OR) with 95% confidence intervals (95% CI) for the GDM and gestational IGT groups compared to controls.

Adjustment was made for maternal age and deliveries.

Table 1.

	GDM (n=306)	Gestational IGT (n=744)	Controls (n=329)
Women			
OGTT, 2-h glucose, mmol/l*	10.7 (10-20)	9.1 (8.6-9.9)	6.5 (3.3-8.5)
Age at delivery, years*	32 (18-46)	32 (17-45)	31 (20-42)
Age at delivery, 35-39 years[†]	83 (27.1)	178 (23.9)	70 (21.3)
Age at delivery, >40 years[†]	24 (7.8)	43 (5.8)	6 (1.8)
Previous deliveries >1[†]	71 (23.2)	140 (18.9)	48 (14.5)
Essential hypertension[†]	8 (2.6)	10 (1.3)	2 (0.6)
Newborns			
Gestational age, weeks*	39.4 (23.9-42.7)	39.7 (29.9-43.0)	40.0 (32.4-43.1)
Birthweight, z-score (SD-units)*	0.12 (-2.95-5.04)	0.16 (-3.46-6.81)	0.17 (-2.36-4.02)
Birthweight, >4499 gram[†]	10 (3.3)	33 (4.4)	15 (4.5)

Table 2.

	GDM (n=306)			Gestational IGT (n=744)			Controls (n=329)
	n (%)	Crude OR	Adjusted OR (95% CI)	n (%)	Crude OR	Adjusted OR (95% CI)	n (%)
Mothers							
Preeclampsia, essential or gestational hypertension	26 (8.5)	3.0	2.7 (1.3-5.8)	46 (6.2)	2.1	2.0 (1.0-4.1)	10 (3.0)
Induction	57 (18.6)	3.4	3.1 (1.8-5.2)	86 (11.6)	1.9	1.8 (1.1-3.0)	21 (6.4)
Forceps or vacuum extraction	20 (6.5)	1.2	1.1 (0.6-2.1)	41 (5.5)	1.0	1.0 (0.6-1.8)	18 (5.5)
Cesarean section,	72 (23.5)	2.3	2.1 (1.4-3.2)	114 (15.4)	1.4	1.3 (0.9-1.9)	39 (11.9)
Elective	7 (8.8)	1.6	1.4 (0.7-2.6)	45 (6.1)	1.1	1.0 (0.5-1.7)	19 (5.8)
Emergency	45 (14.7)	2.7	2.5 (1.5-4.4)	69 (9.3)	1.6	1.5 (0.9-2.6)	20 (6.1)
Infants							
Born <37 gestational weeks	27 (8.9)	3.6	3.6 (1.6-7.7)	39 (5.2)	2.0	2.0 (1.0-4.2)	9 (2.7)
Apgar score <7 at 5 min	8 (2.6)	8.8	9.6 (1.2-78.0)	6 (0.8)	2.7	2.8 (0.3-23.2)	1 (0.3)
Large-for-gestational age infant	26 (8.5)	2.3	2.5 (1.3-5.1)	57 (7.7)	2.0	2.1 (1.1-3.9)	13 (3.9)
Small-for-gestational age infant	6 (2.0)	1.3	1.2 (0.4-4.0)	11 (1.5)	1.0	1.0 (0.3-2.8)	5 (1.5)
Neonatal intensive care >1 day	57 (18.5)	5.2	5.2 (2.8-9.6)	62 (8.2)	2.1	2.1 (1.1-3.8)	14 (4.2)