Maternal and Fetal Outcomes if Gestational Impaired Glucose Tolerance Is Not Treated

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OBJECTIVE — To evaluate whether there is increased maternal or neonatal morbidity in connection with impaired glucose tolerance (IGT) during pregnancy when the condition is not treated.

RESEARCH DESIGN AND METHODS — During the study period of 1997–2001, in a defined geographical area in Sweden, the diagnostic criteria for gestational diabetes mellitus (GDM) were limited to the criteria for diabetes. Prospectively, 213 women who were identified with IGT during pregnancy were undiagnosed and untreated. Data on maternal and fetal outcome was collected from records. For each case subject, four control subjects were taken from the same delivery department.

RESULTS — The proportion of women who underwent cesarean section was significantly higher in the case subjects than in the control subjects and was independently associated with IGT. The adjusted odds ratio (OR) was 1.9 (95% CI 1.2–2.9). The proportion of infants who were large for gestational age (LGA), defined as birth weight >2 SDs greater than the mean for gestation and sex, was independently significantly associated with untreated IGT during pregnancy (OR 7.3, 95% CI 4.1–12.7). Admission to a neonatal intensive care unit (NICU) for 2 days or longer was more common (adjusted OR 2.0, 95% CI 1.1–3.8). However, 71.3% of the children in the IGT group and 87.3% of the control subjects had no neonatal complications.

CONCLUSIONS — There is increased independent association between cesarean section rate, prematurity, LGA, and macrosomic infants born to mothers with untreated IGT. Most of the children were healthy, but there is still increased morbidity. Therefore, to evaluate the effects of treatment, there is a need for a randomized study.

Diabetes Care 26:2107–2111, 2003

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy (1). Originally, the purpose of identifying GDM was the prediction of diabetes later in life (2). Observations that GDM may be associated with an increased risk of fetal malformation and perinatal mortality are likely to be confined to a subgroup of patients with GDM in whom diabetes was present but unrecognized before pregnancy (3,4). Later, the main purpose was to detect women at risk for adverse perinatal outcomes, such as macrosomia, birth trauma, neonatal metabolic abnormalities, and cesarean section (5). In the past decade, however, screening for GDM has been strongly questioned because of the lack of convincing data regarding the possibility to improve these outcomes. Risks associated with GDM have also been attributed to confounding characteristics such as obesity, advanced maternal age, or other medical complications, rather than to the glucose intolerance per se. Identification of impaired glucose tolerance (IGT) during pregnancy has especially been questioned (6–8).

Maternal and fetal complications associated with GDM are often reported from observational studies in which GDM is identified and treated in different ways (9–11). There is, however, a lack of studies of complications when IGT/GDM is not treated. The aim of this study was to evaluate whether there is increased maternal or neonatal morbidity in connection with IGT during pregnancy when the condition is not treated.

RESEARCH DESIGN AND METHODS

— We studied women identified with IGT during pregnancy in the counties of Stockholm and Örebro in Sweden. The study was gradually implemented from 1997 to 2001 by introducing new diagnostic criteria for GDM. Only singleton pregnancies were included. All antenatal care clinics used a two-step screening program for GDM (12). All pregnant women were offered random blood glucose tests performed four to six times during pregnancy. If a random blood glucose level was ≥8.0 mmol/l, a 75-g 2-h oral glucose tolerance test (OGTT) was performed, in accordance with World Health Organization guidelines, within the next few days (13). If this was in early pregnancy and the OGTT was negative, the OGTT was repeated during gestational weeks 28–32. An OGTT during weeks 28–32 was also proposed for

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Received for publication 11 November 2002 and accepted in revised form 23 March 2003.

Abbreviations: GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; LGA, large for gestational age; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test; PIH, pregnancy-induced hypertension.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

women with prior GDM or a prior macrosomic infant (≥4,500 g or greater than or equal to mean + 2 SD). Blood samples, both random and in OGTT, were 5 μl capillary whole blood collected in a microcuvet and immediately analyzed in a Hemocue (Hemocue AB, Ängelholm, Sweden). Results were open in the records. The diagnostic criteria for GDM was fasting blood glucose ≥6.7 mmol/l and/or 2-h blood glucose ≥11.1 mmol/l, which is the diagnostic criteria for diabetes (13). Women diagnosed with GDM or diabetes were referred to special antenatal clinics. Women with OGTT results below the diagnostic criteria for diabetes were considered normal (non-GDM) and were treated in the routine antenatal clinics by midwives; no extra control subjects were suggested.

The results from all OGTTs performed were reported centrally. From these results, women with diabetes as well as IGT were identified. IGT was diagnosed if the fasting blood glucose level was <6.7 mmol/l and the 2-h blood glucose level was 9.0–11.0 mmol/l. This definition of IGT during pregnancy, which is used in several European countries, is a modification of Lind's definition (14). However, the term IGT was never used in the records. Data about the woman, pregnancy, delivery, and child were collected from the records after delivery. Prepregnancy hypertension is defined as hypertension diagnosed before pregnancy, which is noted by the midwife in the Special Antenatal Record with a mark in a check box during the first visit to antenatal care. Pregnancy-induced hypertension (PIH) is defined as blood pressure ≥140/90 mmHg measured twice with at least 6 h. Preeclampsia is defined as blood pressure ≥140/90 mmHg combined with proteinuria at least 1^+ or more on dipstick test of two samples 6 h apart or >0.3 g in a 24-h urine collection. For each woman with untreated IGT, four control subjects were picked from the same delivery department, two before and two after. Information on these individuals came from the diaries of deliveries or attendance at the department.

Statistical analyses were performed using the SPSS statistical software package (SPSS, Chicago, IL). Mann-Whitney *U* or χ^2 tests were used for group comparisons between the IGT patients and the control subjects. Results from women in whom GDM or diabetes was diagnosed are shown as a reference group. Multivariate logistic regression was used to analyze whether there was an independent association between different outcome measurements and untreated IGT. To detect a difference of 5% concerning infants who were large for gestational age (LGA), defined as birth weight >2 SDs greater than the mean for gestation and sex, 156 case subjects and 4 × 156 control subjects were calculated for statistical power (α = 0.05, β = 0.20).

The Ethical Committees of the Medical Faculty at the Karolinska Hospital and Örebro University Hospital approved the study.

Table 1—*Maternal characteristics and complications in the untreated IGT group, control subjects, and women with treated GDM/diabetes*

	Control group (n = 812)	Untreated IGT (n = 213)	P*	GDM/DM (n = 116)
Age (years)	30.0 ± 5.0	32.5 ± 5.0	<0.001	31.4 ± 5.3
Weight (kg)	66.2 ± 11.7	73.4 ± 16.0	<0.001	77.9 ± 16.8
Length (cm)	166 ± 6	163 ± 7	<0.001	163 ± 6
BMI (kg/m^2)	24.1 ± 4.0	27.5 ± 5.4	<0.001	29.4 ± 5.8
Primipara (%)	42.9	33.8	0.02	33.9
Non-Nordic origin (%)	18.8	48.3	<0.001	50.4
Prepregnancy hypertension (%)	0.9	3.8	0.002	6.1
PIH (%)	1.7	2.4	NS	2.6
Preeclampsia (%)	2.7	4.7	NS	6.9
Cesarean section total (%)	14.7	26.4	<0.001	26.7
Emergency	9.8	17.0	0.001	13.8
VE/Forceps (%)	7.9	7.5	NS	6.2

Data are rates or means ± SD. *For control vs. IGT subjects by χ^2 or Mann-Whitney *U* tests.

RESULTS — During the study period, 233 women with IGT diagnosed during pregnancy were identified. Of those women, 20 were excluded because of treatment, with at least self-monitoring of blood glucose documented in their records. This was early in the study period, and treatment had been initiated as a result of earlier policy programs concerning GDM. A total of 116 women with GDM or diabetes were identified.

Maternal characteristics and outcomes are shown in Table 1. The women with IGT were significantly older, had higher BMI, more often had prepregnancy hypertension, and were more often of non-Nordic origin than the control subjects.

The proportion of women with cesarean section was significantly higher than among the control subjects. The crude odds ratio (OR) for cesarean section was 2.1 (95% CI 1.5–3.0), and when adjusted for parity, LGA infant, PIH or preeclampsia, ethnicity, and BMI, OR was 1.9 (1.2–2.9). Regarding emergency cesarean section, the adjusted OR was 2.1 (1.3–3.5).

There were two stillbirths in the IGT group as well as among the control subjects (OR 3.9, 95% CI 0.5–27.5). Both women with IGT were of non-Nordic origin and had slightly increased 2-h blood glucose levels on OGTT (9.2 and 9.4 mmol/l in gestational weeks 28 and 29, respectively). Both children were full term and birth weights were 3,780 and 2,970 g. No neonatal deaths occurred in the group of IGT women, but one neonatal death occurred in the GDM/diabetes mothers because of malformation. Among the control subjects, three neonatal deaths occurred.

Neonatal characteristics among living births are shown in Table 2. Prematurity was significantly higher in the group of IGT women. A multivariate analysis including PIH/preeclampsia, LGA, BMI, chronic hypertension, and ethnicity as covariates showed that IGT was independently (OR 2.0, 95% CI 1.0–3.9) associated with prematurity. The only confounder that was significant in the multivariate analysis was PIH/preeclampsia (3.8, 1.6–9.0). There was a significant difference concerning higher birth weight as well as an increased proportion of macrosomia or LGA infants in the IGT group compared with the control subjects. A multivariate logistic regression analysis of LGA infants was performed, and results

Table 2—*Neonatal characteristics in the untreated IGT group, control subjects, and the women with treated GDM/diabetes*

	Control group (n = 810)	Untreated IGT (n = 211)	P*	GDM/DM (n = 116)
Gestational age (weeks)	39.2 ± 1.9	38.6 ± 1.8	<0.001	38.3 ± 1.9
Prematurity <37 weeks (%)	5.4	11.4	0.005	13.9
Birth weight (g)	3,516 ± 571	3,799 ± 657	<0.001	3,733 ± 681
Macrosomic				
≥4,000 g (%)	16.4	33.0	<0.001	30.4
≥4,500 g (%)	3.3	12.4	<0.001	10.4
≥5,000 g (%)	0.2	4.3	<0.001	4.3
LGA (%)	4.2	24.9	<0.001	25.2
SGA (%)	2.2	0.5	NS	0.9

Data are rates or means ± SD. *For control vs. IGT subjects by χ^2 or Mann-Whitney U tests. SGA, small for gestational age.

are shown in Table 3. LGA infants are independently significantly associated with untreated IGT during pregnancy (7.3, 4.1–12.7). Table 4 shows neonatal morbidity, which was rare in all groups, with no significant difference except for Erb's palsy and hypoglycemia. A significantly higher number of children in the IGT group were admitted to and treated for 2 days or longer at a NICU. Multivariate logistic regression shows an independently higher risk of NICU admission (2.3, 1.3–4.0) (Table 5). Prematurity is a strong mediating factor for NICU admission, but after introduction into the model, IGT still has an OR of 2.0 (1.1–3.8). A total of 71.3% of the children in the IGT group had no neonatal complications, compared with 87.3% of the control subjects.

CONCLUSIONS — The results of the present study demonstrate that IGT is independently and significantly associated with an increased incidence of cesarean section and prematurity as well as a markedly increased proportion of LGA or macrosomic infants and admission to a NICU for 2 days or longer. The design of the present study, with control subjects selected from the same delivery department as the IGT case subjects, was chosen because of possible differences in obstetrical practice between centers.

In the present study, the values of OGTT blood sampling were open and recorded in the antenatal care records. All case subjects were informed that their results of OGTT were normal. All staff members were informed that values below the diabetes level were considered normal. It is unlikely that midwifes or obstetricians at the delivery departments were aware of the OGTT blood glucose results. Every record has been scrutinized to detect and exclude cases in which the woman received special treatment because of OGTT results. The possibility that some patients with prior GDM could have decided to modify their diets on their own could not be excluded. If any effect, it would probably have reduced the proportion of LGA infants.

The power in this study was calculated to detect an absolute increase of 5% in main outcome LGA infants. For pregnancy complications, such as stillbirths, PIH, and preeclampsia, the study cannot exclude differences remaining undetected due to insufficient power.

Roberts et al. (15) evaluated outcomes of women with untreated IGT during pregnancy and found increased incidence of cesarean section but no differences in neonatal outcome compared with women with normal OGTT. In addition to using a lower threshold for IGT (7.8 mmol/l), their group with normal OGTT was characterized by risk factors for GDM. This could explain why their results differ from those of the present study.

There is an ongoing worldwide study, the Hyperglycemia and Adverse Perinatal Outcome (HAPO) (16), which aims to include a group of 25,000 women in which those with IGT will remain untreated (fasting blood glucose level ≤5.8 mmol/l and 2-h blood glucose level 7.8–11.0 mmol/l). There are hitherto no data published from that study.

It has been shown earlier that women from countries outside Sweden have higher risk of perinatal mortality, lower birth weight, and increased incidence of prematurity and cesarean section (17,18).

In the present study, non-Nordic origin reduced the LGA proportion in the IGT group but had no influence on morbidity. Thus, ethnicity influences not only the proportion of women with GDM but also the outcome.

An important finding is that the proportion of women with cesarean section is significantly higher, even after adjust-

Table 3—*Crude and adjusted ORs for LGA infants in IGT women*

	Univariate model		Multivariate model	
	OR	95% CI	OR	95% CI
Control subjects	1.0		1.0	
IGT	7.6	4.7–12.0	7.3	4.1–12.7
BMI				
<25 kg/m^2			1.0	
25–30 kg/m^2			3.4	1.8–6.5
≥30 kg/m^2			5.0	2.5–10.0
Parity				
0			1.0	
1−			2.1	1.2–3.8
Preexisting hypertension				
No			1.0	
Yes			3.5	0.9–13.2
PIH/Preeclampsia				
No			1.0	
Yes			0.7	0.2–2.1
Nordic origin				
Yes			1.0	
No			0.4	0.2–0.7

Table 4—*Neonatal morbidity (%) in the untreated IGT group, control subjects, and the women with treated GDM/diabetes*

	Control group (n = 810)	Untreated IGT (n = 211)	P*	GDM (n = 116)
Apgar score <7 at 5′	1.4	2.9	NS	0.9
Apgar score <5 at 5′	0.5	1.0	NS	0.9
Erb's palsy	0.1	1.9	0.007	0.9
Transient tachypnea	1.8	1.4	NS	6.1
Hypoglycemia†	2.5	7.1	0.001	20.9
Hyperbilirubinemia requiring treatment	4.1	5.7	NS	6.1
Polycytemi requiring treatment	0.2	1.0	NS	—
Admission to NICU 2 days or longer	6.3	18.6	<0.001	28.7
No neonatal complication	87.3	71.3	<0.001	64.6

Data are %. *For control vs. IGT subjects by χ^2 test. †The glucose cut point for hypoglycemia was recommended to be <2.2 mmol/l.

ment for confounders. This finding is in accordance with others (15,19). Contrary to the conclusion by Naylor et al. (19) that it could be the diagnosis per se that led to intervention, the present study indicates an independent association because the obstetrician was not informed of the deviation in glucose tolerance.

The increased proportion of macrosomic infants and morbidity is in accordance with findings already established in a group of women with borderline glucose tolerance (9,20–22). Fetal macrosomia is associated with delivery problems, such as shoulder dystocia and increased risk of cesarean section (23). According to that, the incidence of Erb's palsy is significantly increased in this study, but because it is rare, the population is too small for further analysis. An increased proportion of LGA and macrosomia is a major outcome in GDM, even when treated, and is often used as a reason to detect and manage GDM. The continuous relationship between birth weight and OGTT results demonstrates the difficulties in defining a single cutoff value for the diagnosis of GDM as a biological threshold for risk. In this study, LGA infant was a significant confounder for admission to the NICU for 2 days or longer. LGA infants are often screened routinely for hypoglycemia with a possible positive diagnosis that is not related to symptoms. Because the rate of different diagnoses was low, the number of patients for separate diagnoses was not enough to achieve statistical power. Admission to a NICU, therefore, is used as a measurement of total morbidity. The proportion of cases transferred to a NICU for 2 days or longer is increased. The limit of 2 days or longer is chosen to select cases of morbidity that were not just for short observation. Despite increased incidence of admission to a NICU, 71.3% of the infants were healthy, with no complications, and severe morbidity was rare.

Table 5—*Crude and adjusted OR for transfer to NICU for 2 days or longer*

	Model I		Model II		Model III	
	OR	95% CI	OR	95% CI	OR	95% CI
Control subjects	1.0		1.0		1.0	
IGT	3.4	2.2–5.3	2.3	1.3–4.0	2.0	1.1–3.8
Chronic hypertension						
No			1.0		1.0	
Yes			1.4	0.4–5.6	1.1	0.2–4.9
PIH/preeclampsia						
No			1.0		1.0	
Yes			1.9	0.7–4.6	1.4	0.5–3.6
BMI						
<25 kg/m^2			1.0		1.0	
<25–30 kg/m^2			1.7	1.0–3.0	1.7	0.9–3.1
≥30 kg/m^2			1.8	0.9–3.5	2.2	1.0–4.6
LGA						
No			1.0		1.0	
Yes			2.3	1.2–4.4	2.4	1.1–4.9
Nordic origin						
Yes			1.0		1.0	
No			0.8	0.5–1.5	0.8	0.4–1.5
Prematurity						
No					1.0	
Yes					16.3	8.7–31

The outcome among GDM women diagnosed with diabetes is shown as a reference for obstetrical practice when GDM was diagnosed. Those women with diabetes are all treated, and the outcome despite that was quite similar to the outcome of IGT women and quite different from that of the control subjects. The outcome in the diabetes group could be due to either difficulties to influence the outcome by treatment, or the fact that treatment could have stopped the increased complications noted in this group with greater deterioration in glucose tolerance. This underlines the need for randomized studies of the effects of treatment in women with IGT. The present study could not be used to support the need for treatment of IGT.

The results of this study confirm that there is increased maternal and fetal morbidity in terms of cesarean section rate, preterm delivery, Erb's palsy, and admission to a NICU among women who had untreated IGT during pregnancy. A strong independent association exists between LGA infants and mothers with untreated IGT. Despite increased morbidity, most of the children are healthy. To determine whether there is an effect of treatment, a randomized study is needed.

Acknowledgments— This study was supported by grants from the Research Committee of Örebro County Council.

We thank midwife Susanne Gärdefors of the Department of Obstetrics & Gynecology, Öre-

bro University Hospital, who searched for the records and registered data, and all of the midwives who sent OGTT results and data for protocols during the study.

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