Analiza nosečnic z diagnozo nosečnostna sladkorna bolezen, ki ni bila potrjena z oralnim glukoznim tolerančnim testom v zgodnji nosečnosti

Analysis of pregnant women with the diagnosis of gestational diabetes mellitus without oral glucose tolerance test confirmation in early pregnancy

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Izvleček

Namen: *Cilj analize je ugotoviti delež nosečnic, ki jih je ginekolog napotil v diabetološko ambulanto Univerzitetnega kliničnega centra Maribor pod diagnozo nosečnostna sladkorna bolezen (NSB), temelječo na neustrezno izvedeni meritvi glukoze na tešče (GNT). Dodatno smo želeli primerjati izide nosečnosti med podskupinama, in sicer tisto, ki ji je bila v 24. do 28. tednu nosečnosti z oralnim glukoznim tolerančnim testom (OGTT) potrjena NSB, in tisto, ki smo jo poimenovali brez–NSB. Obe podskupini smo v zgodnji nosečnosti opredelili kot "verjetno NSB ni prisotna".*

Metode: *Retrospektivno smo pregledali dokumentacijo 81 nosečnic, ki so bile napotene v naš center z diagnozo zgodnja NSB. Ker diagnoze s ponovnim testiranjem z OGTT*

Abstract

Purpose: *The aim of this analysis was to determine the proportion of pregnant women referred by gynaecologists to the outpatient diabetes clinic of the University Medical Centre Maribor with a diagnosis of gestational diabetes mellitus (GDM) based on inappropriately measured fasting plasma glucose (FPG). Additionally, we wanted to compare pregnancy outcomes in subgroups diagnosed later as having GDM vs. no–GDM with oral glucose tolerance testing (OGTT) in the 24th to 28th week of pregnancy, but declared as "probably not having GDM" in early pregnancy.*

Methods: *We reviewed retrospectively data on 81 pregnancies referred to our centre, from August 2013 to July 2014, with a diagnosis of early GDM that we did not con-*

nismo potrdili, so bile rutinsko še naprej vodene pri ginekologu. Nosečnice, pri katerih je ginekolog z OGTT v 24. do 28. tednu potrdil NSB, so bile ponovno napotene k diabetologu.

Rezultati: *Povprečna starost celotne skupine je bila 30,5 ± 4,7 let, 91 % je bilo starih ≥ 25 let, 40 % je bilo pred nosečnostjo čezmerno težkih. Obdobje teščosti pred meritvijo GNT, krajše od 8 ur, smo ugotovili pri 36 %. Med podskupinama NSB in brez–NSB je večji delež z NSB poročal o stradalnem obdobju pred meritvijo GNT, krajšem od 8 ur (75 % vs. 32 %; p = 0,022), porodna teža je bila večja v podskupini GDM (3778 ± 588 g vs. 3316 ± 618 g; p = 0,048). V pojavljanju makrosomije, eklampsije, Carskega reza in obporodnih poškodb ni bilo razlik.*

Zaključek: *Ustrezna priprava po protokolu na meritev GNT lahko izboljša natančnost diagnosticiranja zgodnje NSB. Če edina izmerjena GNT v zgodnji nosečnosti le malo presega normalno območje, priporočamo retestiranje z OGTT. Tak pristop najverjetneje nima negativnih učinkov na izide nosečnosti.*

firm with OGTT retesting. After retesting, women were followed up routinely by a gynaecologist, but those with a diagnostic OGTT, performed in the 24th to 28th week, were referred back to a diabetologist.

Results: *The age of the entire cohort was 30.5±4.7 years, and 91% were ≥25 years old; 40% were overweight before pregnancy. The period of fasting before FPG measurement was less than 8 hours in 36%. When comparing the GDM vs. no–GDM subgroups, a higher proportion of women with GDM were fasted for less than 8 hours before FPG measurement (75% vs. 32%; p=0.022), and birth weight was higher for women with GDM (3778±588 g vs. 3316±618 g; p=0.048). There were no differences in macrosomia, eclampsia, Caesarean delivery and birth trauma.*

Conclusion: *The accuracy of the diagnosis of early pregnancy GDM can be improved by following the FPG measurement protocol. When a single FPG in early pregnancy is near normal we suggest retesting with an OGTT. This approach probably has no adverse effect on pregnancy outcomes.*

INTRODUCTION

Diabetes mellitus in pregnant women may be pregestational, with pre–existing type 1 or type 2 diabetes, or hyperglycaemia can be first recognised during pregnancy. The latter cases comprise two distinct categories: gestational diabetes mellitus (GDM) and previously unrecognised pregestational diabetes (1). The prevalence of unrecognised pregestational type 2 diabetes is increasing steeply as a result of women becoming pregnant at older ages (2). Recognition of asymptomatic hyperglycaemia is of high importance because poor glycaemic control during the period of fetal organogenesis carries the risk of a high incidence of spontaneous abortion and congenital anomalies. The risk increases exponentially with increasing glycosylated haemoglobin (HbA1c). On the other hand, the rates of malformation are similar to those in the background population (around 2%) when the early pregnancy HbA1c is within the normal range (3). As the screening test for detection of hyperglycaemia in early pregnancy, determination of fasting plasma glucose (FPG) is performed at the first prenatal visit, usually by a gynaecologist (1). According to the Slovenian guidelines, this screening is mandatory for all pregnant women (4). According to the guidelines, overt diabetes is confirmed in all pregnant women with FPG of 7.0 mmol/L or above. The term "early pregnancy GDM" is used to describe glucose levels in early pregnancy that do not meet standard non–pregnant criteria for overt diabetes, but are diagnostic for gestational diabetes, and are in the range of 5.1 to 6.9 mmol/L. A single deter-

mination of fasting blood glucose is sufficient for the diagnosis (1,4).

The diagnosis of GDM early in pregnancy with a single determination of FPG carries a risk of overdiagnosis of GDM. This is associated with an unnecessary psychological burden on the pregnant woman, unnecessary visits to a diabetologist and unnecessary expenses related to additional laboratory testing and self–monitoring of blood glucose performed by pregnant women during follow–up. Upon referral of pregnant women with a diagnosis of GDM to the outpatient clinic of the University Medical Centre Maribor it was noticed that many women were not properly prepared for glucose testing. This renders the diagnosis of GDM uncertain. It should also be considered that a single determination of FPG, as well as OGTT, is an imprecise test with relatively poor reproducibility (5).

In our retrospective clinical study, we aimed to determine the proportion of pregnant women referred to our outpatient diabetes clinic with diagnosis of GDM based on not properly performed FPG, we excluded with OGTT short after the referral. Correct diagnosis based on properly performed FPG measurement with at least 8 hour fasting period before FPG determination is important clinical issue, that can direct more cost–effective approach and better clinical practise in early pregnancy. Further, we wanted to determine whether there was any difference in the pregnancy outcomes in two subgroups (no–GDM and GDM), as categorised at the 24th week of gestation or later with the OGTT retesting performed by a gynaecologist, but whom we declared as "probably not having GDM" according to the OGTT performed in early pregnancy, short after the referral to our diabetes centre.

MATERIALS AND METHODS

In this retrospective study, we included 81 pregnant women referred to the outpatient diabetes clinic of the University Medical Centre Maribor with a diagnosis of GDM in the first trimester of pregnancy based on FPG determination performed by gynaecologist, but we declared as "probably not having GDM" according to the OGTT performed in early pregnancy, short after the referral to our diabetes clinic.

The eligible women were all pregnant women before 24th week of gestation referred to our diabetes clinic in the period from 1st August 2013 until 31st July 2014 with the FPG in the range of 5.1 to 5.3 mmol/L, or, irrespective of the blood glucose value, but with clear evidence of inappropriate preparation for the glucose determination. At their first visit to our centre, a nurse informed all the eligible women about the proper preparation for blood glucose determination. The instructions were also given in written form. Thereafter, the pregnant women were invited to participate in a short survey that was performed only if the women consented to participate in the study voluntarily. The survey was composed of several important clinical questions that we use in daily practice for pregnant women on their first referral to the diabetologist:

1. the period of fasting before FPG measurement (0–4 hours, 4–8 hours, 8–12 hours, >12 hours)
2. the instructions on proper preparation for FPG measurement that they received from the gynaecologist (3 days of unrestricted food intake, fasting for at least 8–12 hours)
3. week of the current pregnancy
4. age, body weight before pregnancy, body weight at the time of referral, height
5. previous pregnancies (number, year of the birth, gestational week at labour, birth weight and birth length of newborn)
6. family history of diabetes

Women were retested for GDM with the 75–g OGTT in our diabetes centre, short after the referral, but before the 24th week of pregnancy. If the result of the OGTT was normal, we categorised the woman as "probably not having GDM", and all of these women were afterwards followed up by a gynaecologist.

According to the usual clinical practice and Slovenian guidelines, in all pregnant women with normal glucose tolerance in early pregnancy, 75–g

OGTT have to be performed in the 24th to 28th week of pregnancy by a gynaecologist (4). In the case of a normal OGTT in this period of the pregnancy, women were followed by the gynaecologist until delivery. This subgroup of pregnant women we categorised in our retrospective analysis as "no–GDM". In the case of confirmed GDM at the 24th week and beyond, a woman was returned to our outpatient diabetes clinic and followed and treated for GDM until delivery. This subgroup we categorised as "GDM" subgroup.

In the study we determined the proportion of pregnant women that were mistakenly diagnosed as having GDM as a result of to inappropriate preparation for FPG testing by a gynaecologist before their first referral to the outpatient diabetes clinic. Further, we compared the pregnancy outcomes of those with normal glucose tolerance to those with confirmed GDM on the OGTT performed in the 24th to 28th week of pregnancy, but declared as "probably not having GDM" on the basis of the OGTT performed in early pregnancy, shortly after referral to our centre.

STATISTICAL ANALYSIS

The values are presented as continuous variables with the mean + standard deviation (SD). For the evaluation of differences between groups a paired samples t–test was used for continuous variables and the chi square test for categorical variables. P < 0,05 was regarded as statistically significant. SPSS 19.0 software for Windows was used for the statistical analysis.

RESULTS

Demographic data and clinical data for the entire cohort and the subgroups are shown in Table 1. Pregnancy outcome data are shown in Table 2.

Entire cohort

A total of 81 pregnant women, aged 30.5 ± 4.7 years, referred by a gynaecologist with the diagnosis of early pregnancy GDM (GDM before the 24th week of gestation), were included in the retrospective clinical analysis. The proportion of women aged 25 years or older was 91%, and 62% were 30 years of age or older; 40% were overweight (body mass index (BMI) ≥25 kg/m^2) and 14% were obese (BMI ≥30 kg/m^2) before pregnancy. The FPG at referral was 5.24 ± 0.25 mmol/L. The period of fasting before FPG measurement was less than 8 hours in 36%, despite the fact that 83% of all women were properly instructed by a gynaecologist on how to prepare for the glucose measurement.

Subgroups (no–GDM, and GDM at and beyond 24th week of gestation)

The subgroups did not differ according to their age, proportions aged ≥25 years and ≥30 years, family history of diabetes, or FPG. A significantly higher proportion of the GDM group (vs. the no–GDM group) fasted for less than 8 hours before FPG measurement, 75% vs. 32% (p=0.022), respectively, although there were no significant differences in the instructions regarding proper preparation for the FPG measurement between the groups. The subgroups did not differ significantly in BMI, or the proportions overweight and obese, but numerically there were more overweight women in the GDM group: 63% vs. 37%, (p=0.253), respectively.

Perinatal outcomes

The gestational age at birth for the entire cohort, and the no–GDM and GDM groups, was similar, 39.1 ±2.4, 39.0 ±2.5, and 40.0 ±0.9 weeks, respectively. Birth weight was significantly higher in the GDM vs. the no–GDM group: 3778 ±588 g vs. 3316 ±618 g (p=0.048). There were no significant differences in the rate of macrosomia (12.3%, 12.3% and 12.5% for the entire cohort, no–GDM and GDM group, respectively). The rate of Caesarean delivery was 28.7% for the entire cohort, and did not differ significantly between the subgroups, but there was a numerically higher proportion of Caesarean deliveries in the no–GDM vs. the GDM group: 30.6% vs. 12.5% (p=0.427). There were no cases of preeclampsia, eclampsia or birth trauma.

Table 1. *Time to diagnostic procedures and initiation of therapy /delay in diagnostic procedures and initiation of therapy*

	entire cohort (n=81)	No GDM* (n=73)	GDM* (n=8)	p-value for no GDM vs. GDM
Maternal age (years)	30,5 ±4,7	30,1±0,6	31,4 ±1,5	n.s.
Maternal age >25 years, n (%)	74 (91%)	66 (90%)	8 (100%)	n.s.
Maternal age >30 years n (%)	50 (62%)	45 (62%)	5 (63%)	n.s.
Familial history of diabetes n (%)	26 (32%)	23 (32%)	3 (37%)	n.s.
FPG at referral (mmol/L)	5,24 ±0,25	5,24 ±0,03	5,28 ±0,06	n.s.
Fasting less than 8 hours before FPG measurement n (%)	29 (36%)	23 (32%)	6 (75%)	0,022
Properly instructed on preparation for FPG measurement, n (%)	67 (83%)	59 (81%)	8 (100%)	n.s.
Body weight before pregnancy (kg)	68,5 ±15,7	67,9 ±1,8	73,6 ±5,3	n.s.
Body height before pregnancy (cm)	166,0 ±6,1	166,2 ±0,7	164,3 ±2,4	n.s.
BMI before pregnancy (kg/m^2)	26,7 ±2,4	24,6 ±6,6	27,2 ±4,8	n.s.
BMI > 25 kg/m^2 before pregnancy, n (%)	32 (40%)	27 (37%)	5 (63%)	n.s.
BMI > 30 kg/m^2 before pregnancy, n (%)	11 (14)%	10 (14%)	1 (13%)	n.s.

*groups are formed based on retesting at and beyond 24th week
Abbreviations: GDM – gestational diabetes mellitus, FPG – fasting plasma glucose, BMI – body mass index

DISCUSSION

Based on our retrospective analysis, we wish to emphasise that proper preparation for FPG determination is essential for correct and accurate diagnosis of GDM, and can lower the rate of overdiagnosis of GDM in early pregnancy. We compared pregnancy outcomes, with a particular interest in the birth weight, preeclampsia, eclampsia, premature Caesarean delivery, and birth trauma, in a group of women who were diagnosed with GDM vs. a group with normal OGTT at retesting in the 24th week of pregnancy and beyond, all of whom had normal OGTT in early pregnancy.

Overdiagnosis of GDM

Historically, the term "gestational diabetes" was used to categorise women with onset or first recog-

Table 2. *Pregnancy outcomes for the entire cohort and subgroups.*

	entire cohort (n=81)	No GDM* (n=73)	GDM* (n=8)	p-value for no GDM vs. GDM
Gestational age at delivery (weeks)	39,1 ±2,4	39,0 ±2,5	40,0 ±0,9	n.s.
Birth weight (g)	3362 ±627	3316 ±618	3778 ± 588	0,048
**Macrosomia, n (%)	10 (12,3%)	9 (12,3%)	1 (12,5%)	n.s.
Preeclampsia / eclampsia n (%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Birth trauma, n (%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Caesarean delivery, n (%)	23 (28,7%)	22 (30,6%)	1 (12,5%)	n.s.

Abbreviations: GDM – gestational diabetes mellitus
*groups are formed based on retesting at and beyond 24th week
**Macrosomia - birth weight > 4000 g

nition of abnormal glucose tolerance during pregnancy. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus recommended distinguishing women with probable pre–existing diabetes that is first recognised during pregnancy, (so–called "overt diabetes"), from those with transient hyperglycaemia due to pregnancy–related insulin resistance, called "GDM". This recommendation is based on the fact that an increasing proportion of childbearing women have overt but unrecognised type 2 diabetes, due to the increasing prevalence of obesity, lack of routine glucose screening/testing in the fertile period, and the fact that women often become pregnant later in life, which is inevitably related to a higher incidence of type 2 diabetes (1). Data from England have shown an approximately sixfold increase in type 2 diabetes, when comparing the period from 2002 to 2004 with the period from 1996 to 1998 (6). The National Health and Nutrition Examination Survey (NHANES) data from the USA for 2005 to 2008 indicate that childbearing women aged 18–44 years have known diabetes in 2.8%, undiagnosed diabetes in 1.7% and prediabetes (impaired fasting glucose, impaired glucose tolerance) in 26.4%. Overall, 30.9% have disorders of glucose metabolism, and 4.7% have diabetes (7). Based on the results from England and the USA, and well–known projections showing an increasing prevalence of obesity and type 2 diabetes, we expect the prevalence of pregestational diabetes in women of childbearing age to increase further in the following years. Given the increasing prevalence of glucose intolerance, it is desirable to detect disorders of glucose metabolism as early as possible, with a special interest in undiagnosed overt diabetes in pregnancy, because interventions such as diet, medication, and exercise may be applied earlier and have a positive effect on maternal and fetal outcomes (1).

Assessment of glycaemia in early pregnancy would also result in detection of milder degrees of hyperglycemia, less severe than in overt diabetes (1). Recently, two studies reported that higher fasting plasma glucose levels (lower than those diagnostic of diabetes) in the first trimester are associated with increased risks of later diagnosis of GDM and ad-

verse pregnancy outcomes. In an Israelian study, the authors reported an increasing frequency of GDM development, from 1% for those with FPG below 4.2 mmol/L to 11.7% for the group with FPG in the range of 5.6 to 5.8 mmol/L (8). In a Chinese population, the incidence of GDM was 37.0, 52.7, and 66.2%, respectively, for women with FPG at the first prenatal visit of 5.10 to 5.59, 5.60 to 6.09, and 6.10 to 6.99 mmol/L, respectively (9). In our analysis, the frequency of GDM development was 9.9% (8 women out of 81). Our results are similar to the study in Israelian women. The incidence of GDM in their study was 9.4% for pregnant women with an early pregnancy FPG in the range of 5.0 to 5.3 mmol/L (8). Both reported frequencies are below the expected average prevalence of GDM in pregnant women according to the IADPSG criteria for the diagnosis of GDM, based on results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, where the expected average prevalence of GDM is about 18% of all pregnancies (1, 10).

We found that pregnant women referred to our outpatient diabetes clinic by a gynaecologist who were categorised as "probably not having GDM", according to OGTT retesting in the first trimester, were often not prepared properly for the FPG determination. The fasting period before glucose determination was shorter than 8 hours in more than one third, despite the fact that more than 80% of all the pregnant women were properly instructed by a gynaecologist on how to prepare for glucose measurement. We found a higher percentage of inappropriately short fasting periods in the GDM vs. the no–GDM group (p=0.022). We are unable to find a clear explanation for this result, but it may be due to chance. We believe that with retesting we were probably able to exclude early pregnancy GDM in the entire cohort, and in fact we were probably dealing with healthy pregnancies. Because GDM develops during pregnancy in women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state at around and beyond the 24th week of pregnancy, we would not expect the preparation for glucose measurement to have any influence on the later development of GDM. Guidelines recommend at least 8 hours of fasting before fasting glucose measurement or OGTT (11, 12). To avoid overdiagnosis of GDM, there is an urgent requirement for proper preparation for serum glucose determination. We believe the measurement of plasma glucose in the non–fasting state to be a very important bias that causes overdiagnosis of GDM, with important consequences.

In Slovenia, universal screening for overt diabetes in early pregnancy has been implemented (4). This recommendation is based on the fact that only a minority of women of childbearing age can be considered at low risk of GDM. Low risk can be considered only for those younger than 25 years, who are of non–Hispanic white ethnicity, with normal BMI (≤25 kg/m^2), no history of previous glucose intolerance or adverse pregnancy outcomes associated with gestational diabetes, and no first–degree relative with diabetes. In general, BMI ≥25 kg/m^2 is a very important risk factor for diabetes. The American Diabetes Association (ADA) guidelines define women at increased risk of overt diabetes based on BMI ≥25 plus one or more of the following: GDM in a previous pregnancy, HbA1C ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing, first–degree relative with diabetes, high–risk race/ethnicity, history of cardiovascular disease, hypertension, atherogenic dyslipidaemia, polycystic ovary syndrome, physical inactivity, other clinical condition associated with insulin resistance, and previous birth of an infant weighing ≥4000 g (13). We found that a substantial proportion of pregnant women in our study were overweight or obese and older than 25 years, and based on these characteristics were at high risk for GDM. We found a BMI of 25 kg/m^2 or more in 40% of the entire cohort, and in 63% of the women that were in the 24th week of pregnancy and beyond diagnosed with GDM. The proportion of women with BMI ≥25 kg/m^2 was higher, but non–significantly, in the GDM group, (approximately two thirds vs. one third of the subgroup, respectively). The proportion of obese women (BMI ≥30 kg/m^2) was around 14% for the entire cohort as

well as for both subgroups. In addition, more than 90% of women were older than 25 years, and more than 60% were older than 30 years.

According to the guidelines, the diagnosis of GDM in early pregnancy is confirmed with a single FPG value of 5.1 mmol/L or more, but below 7.0 mmol/L (1, 4). Based on this recommendation, measurement error may be another important bias leading to overdiagnosis of GDM in early pregnancy. Analysis of repeated measurements of FPG, 2–h plasma glucose and HbA1c in fasting participants without diabetes found that 2–h plasma glucose had the greatest within–person variability (coefficient of variation 16.7%), and FPG and HbA1c had coefficients of variation of 5.7 and 3.6%, respectively. The proportion of individuals with a fasting glucose value of 7.0 mmol/L or higher on the first test who also had a second glucose value of 7.0 mmol/L or higher was 70.4% (14). According to our results, only 8 out of the 81 women referred to our outpatient diabetes clinic by their gynaecologists with a diagnosis of GDM, based on a single FPG, but with normal glucose tolerance at retesting in early pregnancy, truly developed GDM at or beyond the 24th week of pregnancy. Pregnant women are unnecessarily exposed to a considerable psychological burden related to the misdiagnosis of GDM. Additionally, it has a significant impact on costs and on medical infrastructure capacity (15). Based on the cost–benefit approach and our findings, we believe it is reasonable to retest all pregnant women in early pregnancy when the diagnosis is suspected on the basis of only one FPG in the range of 5.1 to 5.3 mmol/L (in the near vicinity of normal glycaemia for pregnancy). This would parallel the guidelines for the diagnosis of diabetes outside pregnancy, when diabetes in an asymptomatic person is confirmed only on the basis of two diagnostic values, measured on two different days (12).

Outcomes of the pregnancies

We found that the rate of macrosomia (birth weight more than 4000 g) was about 12% in the entire cohort, as well as in the no–GDM and GDM subgroups, with no statistically significant difference between the subgroups. The observed rate of macrosomia is as expected for normal pregnancy without GDM. In the HAPO study the proportion of infants large for gestational weight (birth weight >90th percentile) birthed by women with FPG of 4.5 to 4.9 mmol/L was about 10–13% (10). The rate of macrosomia in the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and a multicentre, randomized study of treatment for mild gestational diabetes (MFMU trial), which compared active treatment vs. standard obstetric care for mild GDM, was higher for the untreated subgroup than in our study, at 21% and 14.3% respectively (16, 17). The birth weight for the GDM subgroup in our study was significantly higher than in the no–GDM group (3778 ± 588 vs. 3316 ± 618, p=0.048). The higher birth weight in the GDM group was probably related to hyperglycaemia in the second part of pregnancy. We found no influence of pre–pregnancy BMI (overweight or obese) on birth weight, as some authors have done (18–20). No other important adverse outcomes associated with diabetes during pregnancy (preeclampsia, eclampsia and birth trauma) were found in our study.

CONCLUSION

Overdiagnosis of GDM in early pregnancy exposes pregnant women to a considerable psychological burden, and can lead to substantial costs and unnecessarily consume medical capacity. The diagnostic accuracy of early pregnancy GDM can be improved by strict following of the FPG and OGTT protocol. When a first FPG measured in early pregnancy is in the near normal range for GDM we suggest retesting with OGTT. This approach seems to have no adverse effect on pregnancy outcomes.

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