UNIL | Université de Lausanne
Faculté de biologie et de médecine

Mémoire de Maîtrise en médecine

Impact of risk factors on maternal outcomes in pregnancies complicated with gestational diabetes mellitus

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Lausanne, 15.02.2019

TABLE DES MATIERES

Abstract

Background

Gestational diabetes mellitus (GDM) is defined as an alteration of the glucose metabolism during pregnancy. GDM is a common pregnancy complication affecting over 17% of all pregnancies and is associated with maternal and neonatal morbidity. Universal screening is widely the norm.

Objective

The present study was performed to investigate the impact of the presence- or lack - of risk factors on maternal outcomes in pregnancies complicated with GDM, during pregnancy and after delivery. We investigated this in the context of a regular care including capillary glucose management, lifestyle modification, treatment if indicated, which may impact some of the outcomes.

Material and methods

This study included 673 pregnant women diagnosed with GDM according to the International Society of Diabetes in Pregnancy Study Group (IADSPG) criteria with a 75g oral glucose tolerance test (OGTT) performed at 24-28 weeks of gestational age.
Anthropometric and metabolic characteristics were assessed for each participant. Risk factors were chosen based on the recommendation of the American Diabetes Association (ADA), their known impact on the risk of GDM, their prevalence and the feasibility to define them clearly in routine clinical care. These included: previous GDM, first degree relatives with type 2 diabetes mellitus (T2DM), ethnicity with high diabetes prevalence, overweight and/or obesity. The presence of maternal, mostly metabolic outcomes such as the need for any medical glucose treatment (regardless if insulin or metformin), HbA1c level, FBG and 2h BG values after the 75g OGTT 6-8 weeks post-partum as well as the mode of delivery were prospectively recorded according to these individual risk factors as well as according to the presence or absence of any risk factor. We tested for normal distribution for continuous variables. Logistic regression and linear regression were used to compare dichotomous variables and continuous variables respectively. Outcomes are expressed as odds ratio and β coefficient. The latter, if statistically significant, means that for every 1-unit increase in the predictive factor, the outcome variable will increase by the β coefficient value.

Results

The mean age was 32.9 (± 5.4). Women with a previous history of GDM had significantly higher values of HbA1c at the first GDM appointment (β coefficient 0.22 [0.11-0.33]), at the end of pregnancy (β coefficient 0.17 [-0.2-0.36]), and at 6-8 weeks post-partum (β coefficient 0.18 [0.08-0.28]). Same was found for fasting blood glucose (FBG) (β coefficient 0.26 [0.10-0.42]), 2h-BG (β coefficient 0.89 [0.42-1.36]) levels during the OGTT at 6-8 weeks post-partum. The need for medical glucose treatment was greater in women with this RF (OR 1.97 [1.07-3.06]).

Women with history of first-degree relatives with T2DM had significantly higher values of HbA1c at the first GDM appointment (β coefficient 0.11 [0.05-0.18]), at the end of pregnancy (β coefficient 0.16 [0.06-0.27]) as well as 2h-BG (β coefficient 0.34 [0.05-0.62]) levels post-partum. The need to treat was greater in women with the RF (OR 1.52 [1.08-2.14]).
Women with a high-risk non-Caucasian ethnicity had higher values of HbA1c at the first GDM appointment (β coefficient 0.09 [0.32-0.17]) and at 6-8 weeks post-partum (β coefficient 0.11 [0.04-0.17]). The same was found for post-partum FBG (β coefficient 0.13 [0.01-0.22]), and 2h-BG (β coefficient 0.45 [0.17-0.72]) levels. Women with this RF were more likely to need medical glucose treatment (OR 1.51 [1.08-2.14]).
Overweight and/or obese women had significantly higher values of HbA1c at the first GDM appointment (β coefficient 0.15 [0.09-0.21]) and at 6-8 weeks post-partum (β coefficient 0.09 [0.04-0.15]). The same was found for FBG (β coefficient 0.27 [0.18-0.36]), 2h-BG (β coefficient 0.33 [0.06-0.59]) levels during the OGTT at 6-8 weeks post-partum. The need for medical glucose-lowering treatment was greater in women with this RF (OR 1.74 [1.26-2.40]).
Obese women had significantly higher values of HbA1c at the first GDM appointment (β coefficient 0.15 [0.07-0.22]), at the end of pregnancy (β coefficient 0.15 [0.01-0.25]), and at 6-8 weeks post-partum (β coefficient 0.11 [0.04-0.18]). The same was found for FBG (β coefficient 0.17 [0.07-0.28]) levels during the OGTT at 6-8 weeks post-partum. The need for medical glucose treatment was greater in women with this RF (OR 1.67 [1.12-2.48]).
Women with at least one risk factor had more likely elevated HbA1c level at the first GDM consultation (β coefficient 0.14 [0.07-0.21]), at the end of pregnancy (β coefficient 0.11 [0.01-0.22]) and at 6-8-week post-partum (β coefficient 0.11 [0.04-0.17]). Similar increase was found for fasting, 1 and 2h-BG. Women with a risk factor were more frequently treated pharmacologically.

Conclusion

Women with an history of GDM and with first degree relative with type 2 diabetes mellitus and women of high-risk ethnicity and overweight/obese women have more frequent adverse pregnancy and maternal metabolic outcomes during and after pregnancy. Surprisingly none of these risk factors are associated with an increase of caesarean delivery in pregnancies complicated with GDM in the setting of routine clinical care and few are associated with a difference of metabolic control at the end of pregnancy.

Keywords: gestational diabetes mellitus, predictive factors, risk factors, maternal outcome.

Introduction

Gestational diabetes mellitus (GDM) is defined as "glucose intolerance with onset or first recognition during pregnancy that does not qualify for diabetes" (1). It is one of the most frequent complication of pregnancy (2). It is associated with adverse health outcomes for the mother and the child (3). Although GDM is limited to pregnancy, and usually disappears after the delivery, the short-term and long-term consequence have medical repercussions. For the offspring, adverse outcomes range from macrosomia, shoulder dystocia, neonatal hypoglycaemia and respiratory distress. Other studies have also shown an increased risk of overweight and the metabolic syndrome in adult offspring of women with GDM (4)-(5). For the mother, this is related to more pregnancy complications, including preeclampsia, higher rates of cesarean section and an increased risk of glucose intolerance postpartum. Moreover, women affected by GDM have 40% higher life-time risk of developing cardiovascular disease (CVD) and type 2 diabetes (T2DM)(6).

GDM is a growing public health concern. The prevalence is rapidly increasing, concomitant to rising rates of obesity, inactivity, older maternal age, and changing diagnostic criteria (7). The prevalence is estimated between 7% and 17% (8). These estimations depend on the population studied, screening methods and diagnostic criteria selected. In Switzerland, the prevalence has been found to be 10.9% (9). The perinatal period is a key moment to intervene to improve the metabolic health. The goal in management of women with GDM is to improve short- and long-term health outcomes for both the mother and the child.
GDM screening and diagnosis has been a subject of debate for decades with conflicting recommendation for universal and selective screening among expert groups. The initial landmark study and cornerstone for diagnostic criteria of GDM was O'Sullivan and Mahan's paper in 1964 (10). Simultaneously to technical advances and scientific research, these criteria have gone through various changes in recent decades. A significant milestone was the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO), a multicentric and prospective study in 2008, designed to investigate the associations of maternal glycemia with risks of adverse pregnancy outcome (11). HAPO study and therefore pave the way for new diagnostic criteria (12). The aim and subsequently the challenge, was defining a pathologic threshold for maternal glycemia values. It consolidated the already known linear association between maternal glycemia and adverse foeto-maternal outcomes. Based on the HAPO study findings, expert opinion and cost-effectiveness, the International Society of Diabetes in Pregnancy Study Group (IADPSG) established new diagnostic cut-off, consequently reaching an international consensus (13). Since then, the IADPSG criteria have been endorsed by WHO (World Health Organisation), FIGO (International Federation of Gynaecology and Obstetrics), the American Diabetes Association (ADA), and several other national diabetes societies. Commonly GDM is now diagnosed by glucose testing with a 75-g Oral Glucose Tolerance Test (OGTT) at 24–28 weeks of gestation in all pregnancies not already diagnosed with overt diabetes or GDM. "Universal screening" was introduced in 2011 in Switzerland the decision is driven by local resources and health care priorities.

GDM is multifactorial disease and, risk factors (RF) are the same as for T2DM (14). The ADA lists overweight (BMI ≥ 25 kg/m^2), first-degree relative with diabetes, high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander), women

diagnosed with a previous history of GDM. Other risk factors are listed in the ADA, which we did not include, namely, hypertension (≥ 140/90 mmHg or on therapy for hypertension), dyslipidaemia, women with polycystic ovary syndrome (PCOS), physical inactivity.

The present study was performed to investigate the impact of the presence - or lack - of risk factors on maternal outcomes in pregnancies complicated with GDM, during pregnancy and after delivery. We investigate this in the context of a regular care, including capillary glucose management, lifestyle modification, treatment if indicated which may impact on some of the outcomes.

Materials and methods

Literature

Exploring scientific literature was the first step in this study. The purpose was to assess the current knowledge/status on the subject. The search engine used was mainly PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Google (http://www.google.ch) using several terms such as "gestational diabetes, GDM risk factors, GDM outcomes, American diabetes association (ADA), diagnostic criteria". Up to date database (http://www.uptodate.com) was an important source to keep up with current knowledge on the topic. In this study, we decided to base ourselves on the "American Diabetes Association Standards of Medical Care in Diabetes 2017" which are similar as the risk factors in the 2019 edition. Pregnant women diagnosed with GDM were analysed based on risk factors from the ADA 2017 guidelines (BMI above 25 kg/m^2, previous GDM, family history of type 2 diabetes mellitus and ethnic family origin with a high prevalence of diabetes). Risk factors were chosen based on the recommendation of the ADA, their known impact on the risk of GDM, their prevalence and the feasibility to define them clearly in routine clinical care. Thus, we did not include hypertension, dyslipidaemia, history of CVD, physical inactivity and the presence of PCOS or known prediabetes

Additionally, to these four risk factors, we included "BMI above 30 kg/m^2" that was a risk factor mentioned by the "National Institute for Care Excellence (NICE) 2016"(15).

Tableau 1 Comparison of risk factor for GDM

NICE	ADA
*Previous gestational diabetes	*Women who were diagnosed with GDM in a previous pregnancy
*Family history of diabetes (first-degree relative with diabetes)	*First-degree relative with diabetes
Minority ethnic family origin with a high prevalence of diabetes	*Members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
*Obesity (BMI >30kg/m^2)	*Overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian Americans**)
Previous macrosomic baby weighing ≥ 4.5 kg	Physical inactivity
	Hypertension (≥140/90 mmHg or on therapy for hypertension)
	HDL cholesterol level ,35 mg/dL (0.90 mmol/L) and/or a triglyceride level .250 mg/dL (2.82 mmol/L)
	Women with polycystic ovary syndrome
	A1C ≥5.7%, IGT, or IFG on previous testing
	Other clinical conditions associated with insulin resistance (e.g. obesity, acanthosis nigricans)
	History of CVD

*Assessed risk factors. ** Not taken into account.

Study population design and setting

The study group consisted of parous women from the endocrinologic and metabolic department at the Centre Hospitalier Universitaire Vaudois (CHUV). This prospective study collected data of 949 pregnant women followed in the endocrinologic and metabolic department at the CHUV between June 2011 and December 2017. The list of participants was obtained through the local database of GDM unit. Medical and clinical data were collected through Soarian, the GDM medical chart and reports of medical and para-medical appointments. The data collected was entered in Secutrial. For each patient age, age of gestation, body mass index (BMI) and weight before pregnancy, weight at the first medical appointment, gravidity, parity, history of GDM, first degree relative with T2DM and ethnicity was assessed. Patients gave their voluntary and informed consent. Parous women who didn't give consent (n=114), who were enrolled in an randomised controlled trial (n=21), with normal OGTT results (n=7), pre-existing type T1DM (n=17) and T2DM (n=23), pre-existing glucose intolerance (n=15), patients with 24-28-week 75g OGTT values indicating a pre-existing diabetes (n=24), women with normal OGTT results (n=7) and lost to follow up (n= 44) were excluded. Moreover, women with undocumented BMI before pregnancy (n=11) were excluded. In total, we excluded 276 women. The final sample included 673 pregnant women.

Screening and GDM diagnostic

The protocol validated in CHUV to diagnose GDM supports the IADPSG position on universal one-step screening. The protocol is based on the ADA 2017 and the IADPSG Consensus Panel 2010 recommendations. All parous women not previously diagnosed with overt diabetes or GDM undergo a 75g oral glucose tolerance test (OGTT), with a fasting, 1h and 2h plasma glucose measurement between the 24-28th weeks of gestation.
According to the IADPSG criteria, GDM is confirmed when:

- fasting blood glucose (FBG) ≥ 5.1mmol
- and/or 1h blood glucose ≥ 10.0 mmol/l
- and/or 2h blood glucose ≥ 8.5 mmol/l (16).

Note that one pathological value is enough to diagnose an onset of GDM. As aforementioned the risk factor selected are the following: BMI above 25 kg/m^2, BMI above 30 kg/m^2, previous GDM, family history of type 2 diabetes mellitus and ethnic family origin with a high prevalence of diabetes. These specific RF were selected for their predictive importance and high frequency in women with GDM, as well as the feasibility to define them clearly in routine clinical care (17)-18-19).

Usual clinical care

Prepartum management

Parous women with an abnormal 75g OGTT between 24-28 week of gestation are referred by the Maternity of the CHUV or their obstetrician/gynaecologist (OB/GYN) for expert care management. The diabetology unit in CHUV is interdisciplinary health-care team, composed of diabetic nurse educators, dietitians, physicians and physiotherapists with expertise in diabetes.
At first clinical appointment the patients were received by a nurse or a physician for an assessment. Pregnant women underwent a medical history taking, a physical and biological examination. During this encounter, attention was also placed on informing and educating the patients on the topic of GDM, importance of diet and physical activity. The women are also trained how to self-monitor blood glucose (SMBG). The women are instructed to self-monitor 4x/day, fasting and 2h after each meal to improve pregnancy outcomes (16). Similar blood glucose targets are recommended national and international societies. Targets for self-monitored glucose control during pregnancy, as recommended by the Société Suisse d'Endocrinologie et de Diabétologie (SSED) 2009, Prise de position Gynécologues et Diabétologue Suisse 2011 and IADPSG 2010 are the following:

- FBG ≤ 5.3 mmol/L
- 1h postprandial ≤ 8 mmol/L
- 2h postprandial ≤ 7 mmol/L

In addition, patients see a dietician experienced in caring for women with diabetes at least once during pregnancy. They receive practical nutrition education and personalised recommendations about their condition and weight gain during pregnancy (20).

They are also actively encouraged to regularly exercise; thus, all participants were offered the possibility to see a physiotherapist to increase their physical activity. The first-line treatment is lifestyle modification through dietary therapy and physical activity.
If despite these measures ≥ 2 blood glucose values are above normoglycemic threshold (FBG ≤ 5.3 mmol/L and/or 2h postprandial ≤ 7 mmol/L) a medical glucose-lowering treatment is initiated.
According to the glucose values and the patient's preferences, insulin is most often the first-line drug for women with GDM after failing to achieve glucose control with lifestyle changes. Insulin type and dose regimens are individualised. Rapid-acting and long-acting insulin are usually combined, therefore mirroring physiologic insulin secretion. Metformin is an alternative.
Finally, according to the metabolic control and the need for medical treatment, labour can be induced between 38-40 weeks' gestation to reduce risk of still birth and caesarean section (21). Any medical glucose-lowering treatment is stopped at delivery.

Post-partum glucose management

Mothers are encouraged to breastfeed immediately after delivery and ideally at least up to 6 months post-partum in prevention of metabolic syndrome and type 2 diabetes in the mother(22). In CHUV 6-8 weeks' post-partum a 75g OGTT FBG and 2h BG was repeated along with Hb1Ac to identify women with metabolic risk such as prediabetes (impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)) as recommended by the ADA and NICE (2015) (see table 2).

Tableau 2. Diagnostic criteria for IGT and diabetes according to ADA (2017) and NICE (2015)

	Normoglycemia	Prediabetes	Diabetes
FBG	< 5.6	5.6-6.9 (IFG)	≥7.0
2h post-prandial, mmol/L	<7.8	7.8-11 (IGT)	≥11.1
HbA1c, %	<5.7	5.7-6.4	≥6.5

Risk factor and outcome measurements

For each participant, biological and clinical parameters were assessed at the first medical appointment. Descriptive variables included age, gestational age, weight and BMI before pregnancy, gravidity and parity, previous pregnancy, Hb1aC, first degree relative with T2DM, and ethnicity. Predictor variable, derived from the ADA 2017 modified with NICE 2015, analysed are:

- previous GDM
- first degree relatives with T2DM
- ethnicity with high diabetes prevalence (Native American, African and African descendant, Latino, Asian American, Pacific Islander)
- overweight and/or obese women based on BMI in comparison to underweight and/or normal weight (ADA, 2017)

- obese women based on BMI in comparison to underweight and/or normal weight and/or overweight women (NICE, 2015)

Outcomes were chosen based on their increased prevalence and the feasibility to define them precisely during routine care. We were specifically interested in maternal outcomes and in metabolic health outcomes. Maternal outcomes accounted for were the need for medical glucose-lowering treatment and the mode of delivery. Metabolic maternal outcome in pregnancy included, both HbA1c value at first GDM visit and at the end of pregnancy. Metabolic maternal outcomes after pregnancy included: HbA1c level, FBG and 2h BG values after the 75g OGTT, all measured 6-8 weeks post-partum.

Statistical analysis

Descriptive statistics included means and standard deviation (SD) for normal continuous variables, numbers and percentages for categorical variables. The normality was verified by the observation of histograms. Logistic regression was used to compare dichotomous variables. Outcome data are presented as odds ratios with 95% confidence intervals, comparing GDM risk factors. Linear regression was used to compare continuous variable. Outcome data is expressed as coefficient beta with 95% confidence intervals. A significative p-value was set to $p<0.05$. Data analysis was performed using Stata (Release 15. College Station, TX: StataCorp LLC) statistical software.
To examine the impact predictive factors on pregnancy and maternal outcomes, participants were divided in two groups for each risk factor assessed. On one hand women with the risk factor and on the other women without the risk factor in question. Note that patients with undocumented and missing data are considered risk free, as clinicians must report risk factor in history taking.

Results

Patients' characteristics at the first consultation are shown in Table 3a. A total of 946 women were identified. We analysed date from 673 women diagnosed with GDM. Their mean age was 32.9 ± 5.4 [range 18-54] years. The first visit was on average at 28.5 ± 3.5 week of gestation. The average BMI before pregnancy was 26.1 kg/m^2, with half of the women being "underweight and normal weight", 28 % were "overweight" defined as BMI ≥25 and <30 kg/m^2 and 22% of the women were considered "obese" (BMI ≥ 30 kg/m^2). Note no adjustment was made for Asian, the ADA and several studies have recommended lowering BMI cut point for overweight to 23 kg/m^2(23). The distribution of parity was normal. The mean parity was primipara, with an average of about 2.6 gravida.
The sample was heterogenous population in terms of origins. The sample population consisted of 404 Caucasians including 201 Swiss patients. Among the 243 high-risk population we identified 110 Africans, 95 Asians, 34 south Americans, 2 central Americans and 2 Pacific islanders. 26 were missing or undocumented and filed as "low-risk ethnicity".

Table 3a. Descriptive characteristics at baseline

Characteristics	n	Mean (SD) or N (%)
Weeks of gestation	671	28.5 (3.5)
Age, years	673	32.9 (5.4)
BMI before pregnancy, kg/m^2	673	26.1 (5.4)
Underweight and normal weight, %	338	50.2
Overweight, %	187	27.8
Obesity, %	148	22
Weight before pregnancy, kg	661	70.2 (16.1)
Gravidity	673	2.54 (1.6)
Parity	386	1.64 (0.9)
GDM in previous pregnancy, yes/no	420	63/357, (15.0/85.0)
First grade family history of T2DM, yes/no[b]	673	218/455 (32.4/67.6)
High-risk ethnicity, yes/no	673	243/430 (36.1/63.9)
Weight at RDV1[e], kg	645	80.6 (16.2)
HbA1c at RDV1[e], %	634	5.5 (0.4)

SD indicates standard deviation

a. underweight <18.5 kg/m^2, normal range 18.5-24.99 kg/m^2, overweight ≥25-30 kg/m^2, obesity ≥30 kg/m^2

b. "no" includes no history of GDM. The "undocumented" answers were assumed as "no" as clinicians must check the presence of this risk factor

c. 1st degree relatives include, mother, father, sister, brother, daughter, son. The "undocumented" answers were assumed as "no" as clinicians must check the presence of this risk factor

d. high-risk ethnicity denotes nationality from the following areas in the world: Africa, Central America, South America, East Asia, West Asia, Oceania. "No" means low risk ethnicity such as North America, East Europe, West Europe (incl. Switzerland). Undocumented answers were not included.

e. denotes first GDM visit

Table 3b. Descriptive characteristics at follow-up

	n	Mean (SD) or N (%)
Need for treatment[a], yes/no	673	349/324 (51.9/48.1)
Mode of delivery[b]	654	266/388 (40.7/59.3)
HbA1c end of pregnancy[c]	236	5.6 (0.4)
HbA1c pp[d]	612	5.4 (0.4)
FBG pp[d]	611	5.1 (0.6)
2h BG pp[d]	604	5.6 (1.7)

SD indicates standard deviation, pp denotes postpartum

a. refers to the need to pharmacologically treat GDM. "Yes" includes all following drugs: metformin, insulin or combination of both.

b. includes childbirth by vaginal delivery, undocumented or missing data are not included

c. refers to HbA1c measured at the end of pregnancy

d. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

Pregnancy outcomes and descriptive characteristics during follow-up are presented in Table 3b.
In the study population, about 52% were pharmacologically treated which included, fast-acting insulin, long-acting insulin and/or metformin. Forty-eight percent were solely treated with lifestyle modification, including nutritional adaptation and physical activity.
Considering the ADA risk factors assessed, twenty-three percent (n=156) of the women diagnosed with GDM had zero risk factor. All in all, seventy-seven percent (n=517) of the pregnant women with GDM had at least one of the risk factors studied.
When the NICE guidelines were applied, thirty-two percent of women (n=215) with GDM had zero of the assessed risk factors. Sixty-eight percent of women (n=458) with GDM had at least one of the risk factors analysed.

Pregnancy and maternal adverse metabolic outcomes regarding previous GDM as a predictive factor are reported in Table 4.
HbA1c values were higher at first GDM visit in the group with personal GDM history, but not at the end of pregnancy. Pharmacologic treatment is also initiated significantly more frequently in this group.

Table 4. GDM history as a predictor factor

Outcome	Women without previous GDM (n=610)	Women with previous GDM (n=63)	β (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.45 (0.40)	5.67 (0.49)	0.22 (0.11-0.33)	<0.0001
HbA1c end of pregnancy[b] Mean (SD)	5.55 (0.39)	5.72 (0.42)	0.17 (-0.20-0.36)	0.072
Need for treatment, yes/no, N (%)	309/244 (55.90/44.10)	40/16 (71.43/28.57)	1.97* (1.08-3.06)	0.027
Caesarean vs vaginal N (%)	200/276 (42.02/57.98)	20/27 (42.55/57.45)	1.02* (0.56-1.87)	0.943
HbA1c pp[c] Mean (SD)	5.37 (0.37)	5.55 (0.39)	0.18 (0.08-0.28)	0.001
FBG pp[c] Mean (SD)	5.00 (0.54)	5.26 (0.74)	0.26 (0.10-0.42)	0.001
2h BG pp[c] Mean (SD)	5.53 (1.59)	6.42 (2.27)	0.89 (0.42-1.36)	<0.0001

a. refers to HbA1c measured at the first GDM visit
b. refers to HbA1c measured at the end of pregnancy
c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

There is no difference in the rate of caesarean sections. However, HbA1c and 75g OGTT values (FBG, 2h- BG) were significantly higher in the group of “women with previous GDM”.

Pregnancy and maternal adverse metabolic outcomes regarding first degree relative with T2DM as a predictive factor are reported in Table 5.

HbA1c levels during pregnancy are significantly higher in the group with a positive family history for T2DM than in the group without, both at the first GDM visit and at the end of pregnancy. These women also present a 52% more frequent need to treat.

There is no difference in the rate of caesarean section. The women with first degree relatives with T2DM have higher values in post-partum 2h BG 75g OGTT.

Table 5. First degree relative with T2DM as a predictor factor

Outcome	No first degree relative with DM2 (n=455)	First degree relative with DM2 (n=218)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.34 (0.39)	5.55 (0.42)	0.11 (0.05-0.18)	0.001
HbA1c end of pregnancy[b] Mean (SD)	5.50 (0.35)	5.66 (0.45)	0.16 (0.06-0.27)	0.002
Need for treatment, yes/no, N (%)	216/185 (53.87/46.13)	133/75 (63.94/36.06)	1.52* (1.08-2.14)	0.017
Cesarean vs vaginal N (%)	153/210 (57.8/42.2)	67/93 (41.9/58.1)	0.99* (0.68-1.44)	0.953
HbA1c pp[c] Mean (SD)	5.38 (0.37)	5.42 (0.38)	0.04 (-0.2-0.10	0.196
FBG pp[c] Mean (SD)	5.01 (0.58)	5.06 (0.53)	0.05 (-0.04 -0.15)	0.287
2h BG pp[c] Mean (SD)	5.49 (1.64)	5.83 (1.75)	0.34 (0.05-0.62)	0.019

a. refers to HbA1c measured at the first GDM visit
b. refers to HbA1c measured at the end of pregnancy
c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

Pregnancy and maternal adverse metabolic outcomes regarding high-risk ethnicity as a predictive factor are reported in Table 6. The pregnant women in the high-risk ethnicity had higher HbA1c levels at first GDM visit, but not at the end of pregnancy. The need to treat considerably higher in women in this high-risk ethnicity group.

Table 6. High risk ethnicity as a predictor factor

Outcome	Low-risk ethnicity[1] (n=430)	High-risk ethnicity[2] (n=243)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.44 (0.41)	5.52 (0.40)	0.09 (0.32-0.17)	0.004
HbA1c end of pregnancy Mean (SD)[b]	5.54 (0.40)	5.61 (0.39)	0.084 (-0.03-0.19)	0.143
Need for treatment, yes/no, N (%)	210/174 (54.7/45.3)	153/93 (62.1/37.9)	1.51* (1.08-2.14)	0.017
Cesarean vs vaginal N (%)	130/196 (39.8/60.2)	98/122 (44.55/55.45)	1.24* (0.87-1.79)	0.231
HbA1c pp[c] Mean (SD)	5.35 (0.37)	5.44 (0.38)	0.11 (0.04-0.17)	0.001
FBG pp[c] Mean (SD)	4.98 (0.49)	5.09 (0.64)	0.13 (0.03-0.22)	0.007
2h BG pp[c] Mean (SD)	5.45 (1.59)	5.87 (1.84)	0.45 (0.17-0.72)	0.001

1. "low risk ethnicity" comprises north Americans, east and west Europeans
2. "high risk group" denotes nationalities from Africa, central America, south America, east Asia, west Asia and Oceania
a. refers to HbA1c measured at the first GDM visit
b. refers to HbA1c measured at the end of pregnancy
c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

There is no difference in the rate of caesarean sections. The women with high-risk ethnicity have higher postpartum HbA1c and 75g OGTT (FBG and 2h BG) values.

Pregnancy and maternal adverse metabolic outcomes regarding overweight/obesity as a predictive factor are reported in Table 7.
HbA1c values at the first GDM visit, but not at the end of pregnancy, were significantly higher in the group of overweight/obese women than in the normal-weight counterparts. Likewise, pharmacologic treatment is 74% significantly more frequent in this group.
There is no difference in caesarean section. Postpartum metabolic control values- HbA1c, FBG and 2h BG after 75g OGTT- are higher in overweight/obese women.

Table 7. Overweight and obesity as a predictor factor

Outcome	BMI <25kg/m^2 (n=338)	BMI ≥ 25kg/m^2 (n=335)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.39 (0.37)	5.55 (0.43)	0.15 (0.09-0.21)	<0.0001
HbA1c end of pregnancy Mean (SD)[b]	5.52 (0.38)	5.59 (0.41)	0.077 (-0.02-0.18)	0.138
Need for treatment, yes/no, N (%)	152/149 (50.5/49.5)	197/111 (63.96/36.04)	1.74* (1.26-2.40)	0.001
Cesarean vs vaginal N (%)	110/149 (42.5/57.5)	110/154 (58.33/41.67)	0.97* (0.68-1.37)	0.852
HbA1c pp[c] Mean (SD)	5.34 (0.37)	5.44(0.37)	0.09 (0.04-0.15)	0.002
FBG pp[c] Mean (SD)	4.89 (0.51)	5.16 (0.59)	0.27 (0.18-0.36)	<0.0001
2h BG pp[c] Mean (SD)	5.44 (1.59)	5.76 (1.75)	0.33 (0.06-0.59)	0.017

a. refers to HbA1c measured at the first GDM visit

b. refers to HbA1c measured at the end of pregnancy

c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

Pregnancy and maternal adverse metabolic outcomes regarding obesity as a predictive factor are reported in Table 8. HbA1c levels during pregnancy are significantly higher in the group of obese women than in the nonobese group, both at the first GDM visit and at the end of pregnancy. These women also present a 67% more frequent need to treat.

Table 8. Obesity as a predictor factor

Outcome	BMI <30kg/m^2 (n= 525)	BMI ≥ 30kg/m^2 (n=148)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.44 (0.39)	5.59 (0.46)	0.15 (0.07-0.22)	<0.0001
HbA1c end of pregnancy Mean (SD)[b]	5.54 (0.37)	5.66 (0.48)	0.13 (0.01-0.25)	0.045
Need for treatment, yes/no, N (%)	257/214 (54.6/45.4)	92/46 (66.7/33.3)	1.67* (1.12-2.48)	0.012
Cesarean vs vaginal N (%)	167/241 (40.9/59.1)	53/62 (46.1/53.9)	1.23* (0.81-1.87)	0.323
HbA1c pp[c] Mean (SD)	5.37 (0.37)	5.47 (0.38)	0.11 (0.04-0.18)	0.003
FBG pp[c] Mean (SD)	4.99 (0.57)	5.16 (0.54)	0.17 (0.07-0.28)	0.002
2h BG pp[c] Mean (SD)	5.58 (1.71)	5.69 (1.56)	0.11 (-0.21-0.44)	0.496

a. refers to HbA1c measured at the first GDM visit

b. refers to HbA1c measured at the end of pregnancy

c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

The is no difference in the rate of caesarean section. However, HbA1c and FBG after the 75g OGTT values were significantly higher in the group of obese women.

Pregnancy and maternal adverse metabolic outcomes regarding all risk factors together according to ADA 2017, using overweight as a risk factor, are reported in Table 9. HbA1c levels at first GDM visit are significantly higher in the group with the risk factors than in the group without, but not at the end of the pregnancy. Pharmacologic treatment is also initiated 87% more frequently in this group**.**

Table 9. All RF together as predictive factors according to ADA 2017 (using overweight as a RF)

Outcome	No RF_25 (n=156)	All RF_25 (n=517)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.38 (0.35)	5.50 (0.42)	0.14 (0.06-0.22)	0.001
HbA1c end of pregnancy Mean (SD)[b]	5.51 (0.36)	5.58 (0.41)	0.08 (-0.04-0.2)	0.196
Need for treatment, yes/no**,** N (%)	69/76 (47.59/52.41)	293/191 (60.54/39.46)	1.87* (1.26-2.79)	0.002
Cesarean vs vaginal N (%)	57/78 (42.22/57.78)	171/240 (41.61/58.39)	0.93* (0.61- 1.42)	0.743
HbA1c pp[c] Mean (SD)	5.32 (0.37)	5.41 (0.37)	0.11 (0.03-0.18)	0.004
FBG pp[c] Mean (SD)	4.85 (0.44)	5.08 (0.59)	0.27 (0.16-0.38)	<0.0001
2h BG pp[c] Mean (SD)	5.31 (1.63)	5.71 (1.72)	0.51 (0.18-0.84)	0.002

This table compares the outcome in groups without and with at least one risk factor (RF) according to the criteria from ADA 2017 (with BMI ≥25 kg/m^2).

a. refers to HbA1c measured at the first GDM visit

b. refers to HbA1c measured at the end of pregnancy

c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

There is no difference in the rate of caesarean sections. HbA1c and 75g OGTT values (FBG, 2h-glucose) were significantly higher in the group with risk factors.

Pregnancy and maternal adverse metabolic outcomes regarding all risk factors together according to NICE 2015, using obesity as a risk factor, are reported in Table 10.
HbA1c levels, both at first GDM visit and at the end of the pregnancy, were significantly with risk factors than the group without. Medical glucose treatment is 66% more frequent in the former group.

Table 10. All RF as predictive factors according to NICE 2015 (using obesity as RF)

Outcome during pregnancy	No RF_30 (n=215)	All RF_30 (n=458)	Beta (95 % CI) or OR* (95% CI)	p-value
HbA1c RDV1[a] Mean (SD)	5.39 (0.35)	5.51 (0.43)	0.14 (0.07-0.21)	<0.0001
HbA1c end of pregnancy [b] Mean (SD)	5.49 (0.34)	5.60 (0.42)	0.11 (0.01-0.22)	0.040
Need for treatment, yes/no, N (%)	98/98 (50/50)	264/169 (60.97/39.03)	1.66* (1.16-2.37)	0.005
Cesarean vs vaginal N (%)	72/109 (39.78/60.22)	156/209 (42.74/57.26)	1.12 *(0.76-1.64)	0.560
HbA1c pp[c] Mean (SD)	5.32 (0.35)	5.42 (0.38)	0.11 (0.04-0.17)	0.001
FBG pp[c] Mean (SD)	4.91 (0.46)	5.08 (0.60)	0.19 (0.09-0.29)	<0.0001
2h BG pp[c] Mean (SD)	5.37 (1.57)	5.74 (1.76)	0.44 (0.14-0.73)	0.003

This table compares the outcome in groups without and with at least one risk factor (RF) according to the criteria from NICE 2015 (with BMI ≥30 kg/m^2).

a. refers to HbA1c measured at the first GDM visit

b. refers to HbA1c measured at the end of pregnancy

c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

Once again, there is no difference in the rate of caesarean sections. The women in the group with risk factors have higher postpartum metabolic control values, both HbA1c and 75g OGTT (FBG and 2h BG).

A summary of pregnancy and maternal adverse metabolic outcomes and all the risk factors assessed are presented in Table 11.

Table 11. Summary of results

Predictive factors Outcomes	GDM history	First degree relative with T2DM	High risk ethnicity	Overweight and obese	Obese	All RF_25[1]	All RF_30[2]
HbA1c RDV1[a]	+	+	+	+	+	+	+
HbA1c end of pregnancy[b]	-	+	-	-	+	-	+
Need for treatment	+	+	+	+	+	+	+
Caesarean vs vaginal	-	-	-	-	-	-	-
HbA1c pp[c]	+	-	+	+	+	+	+
FBG pp[c]	+	-	+	+	+	+	+
2h BG pp[c]	+	+	+	+	-	+	+

1. comparing the outcome in groups without and with at least one risk factor (RF) according to the criteria from ADA 2017 (with BMI ≥25 kg/m^2)

2. comparing the outcome in groups without and with at least one risk factor (RF) according to the criteria from NICE 2015 (with BMI ≥30 kg/m^2)

a. refers to HbA1c measured at the first GDM visit

b. refers to HbA1c measured at the end of pregnancy

c. denotes 6-8 weeks postpartum during a 75 g oral glucose tolerance test

Discussion

GDM is a common condition with rising prevalence associated with higher maternal and neonatal complication. GDM is also responsible for higher lifetime morbidity for both the child and the mother. Diagnosis and adequate treatment of this condition is now part of the usual care (20-24). Debates are still ongoing regarding the optimal screening procedure; shall we screen all women or a selected group of pregnant women. The IADPSG consensus panel serves "as the basis for internationally endorsed criteria for the diagnosis and classification of diabetes in pregnancy"(13). This panel recommends universal screening using a 75g OGTT at 24-28 weeks of gestational age. However, as a result, the total incidence of GDM and therefore immediate therapeutic cost will rise. Financial constraints and public health priorities are important factors in the decision making. Cost effectiveness and the financial impact of the 2011 IADPSG recommendation have been largely discussed (25-26-2).

The present study was performed to investigate the impact of the presence - or lack - of risk factors on maternal outcomes in pregnancies complicated with GDM, during pregnancy and after delivery. Following the ADA or NICE recommendation, women without risk factor make up, about 23% or 32% respectively, of the study population, which is rather low. Our findings, regarding pregnancy outcomes, are that regardless of the type of risk factor, women with risk

factor had higher HbA1c levels at the first appointment at the GDM clinic. For some risk factors, namely first-degree relatives with T2DM and obesity, HbA1c levels at the end of pregnancy were also higher. Women with RF were more likely to be pharmacologically treated and this, too, is seen for any of the risk factors. However, we found no significant difference in caesarean sections rates according to the presence of risk factor. Having a GDM history, a first degree relative with T2DM, being of a high-risk ethnicity or being obese were associated with adverse postpartum metabolic outcome.
Certain differences during pregnancy between women with and without RF were found in all situations, regardless of the RF: These were HbA1c at the first GDM meeting and the need for medical treatment. That means that indeed women with RF come into the treatment centre with a riskier metabolic profile. Importantly, 48% of women without any risk factor according to the ADA criteria still needed medical treatment. This argues more for a need for universal screening.

Surprisingly, none of the risk factor studied in this paper, demonstrated an association between the mode of delivery (c-section) and the analysed risk factor (27). This can be explained as all women, regardless of the presence or absence of their RF, have the same goals regarding weight gain, glucose thresholds etc and that women with RF have more frequently medical treatment in order to improve their outcomes. This may thus have diluted the difference of C-section which is rather a hopeful finding.

The postpartum evaluations are performed 6-8 weeks after delivery, thus 6-8 weeks after the stop of all glucose self-control and medical treatment and clinical follow-up. At this moment, almost all situations show that women with RF have higher metabolic values and thus are at higher risk. This concerns HbA1c, FBG and 2h values after the 75g OGTT. This is important, as 1/3 of women have prediabetes at 1-year postpartum and the values in the early postpartum phase are predictive for the 1-year postpartum values (28). This might implicate that women with RF should need a more intense follow-up and lifestyle intervention in the post-partum phase which is not always easy to implement.

The strength of our study includes the quality outcome data extracted from medical records and the representativity of the population. As for limitations, we performed multiple testing and did not adjust for this. This would have been more complicated in the setting of a master thesis. Similarly, we did not adjust for confounder variables such as age, gestational age, previous parity etc. Other limitations are that we included only four risk factors of the known risk factors for diabetes. Therefore, we are unable to capture the overall impact of GDM, a multifactorial and complex disease. This choice was made after reviewing literature and singling out the most important risk factors (25-26-27-29). Ethnicity and BMI are among RF with strong impact on pregnancy outcomes (25). History of GDM and history of first-degree relatives with T2DM are one of the most important risk factors for developing GDM. Other reasons to choose these RF were their prevalence, for example for overweight and obesity and the feasibility to define these risk factors clearly and precisely in routine clinical care. This was for example more difficult for physical inactivity. Studying the relationship between risk factors and outcomes in a clinical setting where all women are treated with glucose self-control, lifestyle changes and medical treatment as needed, also implies that certain outcomes will be adapted, or the impact diluted. Performing a randomized trial were in one arm all

women are screened and treated and in the other only women with risk factors could give us a clearer answer but would be challenging to perform.

Conclusion

Women with a history of GDM and with first degree relative with type 2 diabetes mellitus, women of high-risk ethnicity and overweight/obese women have more frequent adverse pregnancy and maternal metabolic outcomes during and specifically after pregnancy. Importantly, although lower than for women with RF, the need for medical treatment is very high in women without any RF. Surprisingly none of these risk factors are associated with an increase of caesarean section in pregnancies complicated with GDM in the setting of routine clinical care (30) and few are associated with a difference of metabolic control at the end of pregnancy. This could mean that current clinical care can abolish some of the higher risk during pregnancy such as differences in metabolic control at the end of pregnancy and the need for caesarean section, but not differences in the postpartum period. This could implicate that women with RF should have a more intense follow-up and intervention in the postpartum period. It is worth recognising RF at diagnosis and throughout pregnancy and therefore customise care management in order to prevent adverse outcomes.

Acknowledgement

I would like to express my sincere gratitude to Prof. Puder for her effective supervision with high pedagogical values. I am very grateful for their precious time she offered me during the conception and execution of this work.

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