Cardiometabolic and mental health in women with early gestational diabetes mellitus: A prospective cohort study

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Abstract

Context: Early diagnosis and treatment of gestational diabetes (GDM) may reduce adverse obstetric and neonatal outcomes, especially in high-risk women. However, there is a lack of data for other outcomes.

Objective: We compared cardiometabolic and mental health outcomes in women with early (eGDM) and classical (cGDM) GDM.

Methods: This prospective cohort included 1185 women with cGDM and 76 women with eGDM. eGDM had GDM-risk factors (BMI >30kg/m^2, family history of diabetes, history of GDM, ethnicity), were tested at <20 weeks gestational age and diagnosed using ADA prediabetes criteria. Women underwent lifestyle adaptations. Obstetric, neonatal, mental, cardiometabolic outcomes were assessed during pregnancy and postpartum.

Results: eGDM had lower gestational weight gain than cGDM (10.7±6.2 *vs* 12.6±6.4, p=0.03), but needed more medical treatment (66% *vs* 42%, p<0.001). They had similar rates of adverse maternal and neonatal outcomes, except for increased large-for-gestational-age infants (25% *vs* 15%, p=0.02). Mental health during pregnancy and postpartum did not differ between groups. eGDM had more atherogenic postpartum lipid profile than cGDM (p≤0.001). In eGDM, the postpartum prevalence of metabolic syndrome (MetS) was 1.8-times, prediabetes was 3.1-times and diabetes was 7.4-times higher than cGDM (MetS-waist circumference-based: 62% *vs* 34%/MetS-BMI-based: 46% *vs* 24%; prediabetes: 47.5% *vs* 15.3%; diabetes: 11.9% *vs* 1.6%, all p<0.001). These differences remained unchanged after adjusting for GDM-risk factors.

Conclusion: Compared to cGDM, eGDM was not associated with differences in mental health, but with increased adverse cardiometabolic outcomes, independent of GDM-risk factors and gestational weight gain. This hints to a pre-existing risk-profile in eGDM.

Keywords: GDM-risk factors; Cardio-metabolic; Early gestational diabetes; Metabolic syndrome; Postpartum; Mental health

Introduction

Clinical care can reduce the adverse obstetric and neonatal outcomes observed in gestational diabetes mellitus (GDM) (1,2). Despite this, women with GDM face increased long-term risks, such as excess weight retention, recurrent GDM, depression, diabetes and cardiovascular risks (3–6). International guidelines recommend routine universal screening for GDM between 24-28 weeks gestational age (GA) (7,8). However, there is no international consensus regarding the screening strategy and the diagnostic criteria for early GDM (eGDM) (9), nor is there any consensus if all or only high-risk women should be screened (10–13). Specifically, the recommendations of the World Health Organization (WHO), International Association of Diabetes and Pregnancy Study Groups (IADPSG), and the National Institute for Health and Care Excellence (NICE) regarding screening before 24 weeks GA differ, which considerably complicates the definition of eGDM (8,14,15). As fasting glucose decreases in the first trimester and in the beginning of the second trimester, the initially proposed threshold of fasting plasma glucose (FPG) ≥5.1 mmol/l to diagnose eGDM has been questioned due to its low specificity to diagnose classical GDM (cGDM) (9,12,13). Some authors propose to use the ADA prediabetes criteria FPG ≥5.6 mmol or HbA1c ≥5.7%) to diagnose eGDM in the first trimester (7), though alternative cut-offs, such as FPG of ≥5.5 mmol/l and/or HbA1c ≥5.9%, have also been suggested (12).

Many (15-70%) women with GDM have evidence of hyperglycemia before diagnosis (13). A recent meta-analysis of 13 cohort studies showed that women with eGDM had higher rates of perinatal mortality, neonatal hypoglycemia and insulin use compared to women with classical GDM (cGDM), despite clinical follow-up and treatment (16). Early detection of GDM in high-risk patients provides an excellent and timely opportunity for early intervention and may help to

improve obstetric and neonatal outcomes (17). Women with eGDM could benefit from as many as 14 additional weeks of medical care including lifestyle adaptations to reduce fetal exposure to hyperglycemia compared to those diagnosed later in pregnancy (18), though randomized controlled trials (RCTs) are needed. In contrast, a recent RCT of 962 women that screened obese women between 14-20 weeks GA showed that early detection and general medical treatment (using FPG≥5.3 mmol/l as diagnostic criteria and without a specific focus on lifestyle changes) did not reduce the rates of composite perinatal outcomes compared to women with cGDM (19). In general, there remains a potential risk of overdiagnosis and overtreatment, depending on the diagnostic criteria used to diagnose eGDM.

The relationship between poor mental health including symptoms of depression, well-being and eating behaviors and later development of GDM is well established (20,21). However, there is a lack of data on mental health outcomes during pregnancy and in the postpartum in women with eGDM. Concerning metabolic health in the postpartum period, we are aware of a few, mostly retrospective studies that showed higher rates of abnormal glucose tolerance in the postpartum in women diagnosed with eGDM compared to cGDM (22–24). However, the overall low postpartum testing rates of around 50% limit the interpretation of their findings and they do not comment on cardiovascular risk factors. Recent reports suggest that despite the relatively young age, women with cGDM have a two-fold increased risk of cardiovascular diseases and events in the postpartum even in the absence of diabetes (5,6). However, no study has investigated the cardiovascular profile in eGDM women. Further knowledge about these outcomes would help to guide interventions and management in women with eGDM. The main aim of this study was to characterize the cardiovascular, metabolic and mental health outcomes in pregnancy and in the postpartum in high-risk women with eGDM compared to those with cGDM.

Methods

Study design and patient population

This prospective clinical cohort study followed women with GDM during pregnancy and in the postpartum period between 2011-2021 (25,26). The Human Research Ethics Committee of the Canton de Vaud (326/15) approved the study protocol. Out of the total cohort population of 1687 women with GDM attending antenatal diabetes care at the Woman-mother-child department at the Lausanne University Hospital, 1505 consented to participate indicating a response rate of 89%. For this analysis, we excluded those with known type-1 diabetes (n=16), type-2 diabetes (n=24), who did not attend the scheduled 6-8 weeks postpartum follow-up visit or were not yet due for the visit (together n=204/1505; 14%). Thus, 86% of the women who consented (n=1261) and had valid postpartum data were included in the final analysis. Figure 1 shows the detailed flow chart of the study.

GDM diagnosis, treatment and patient follow-up

Women were diagnosed with cGDM if one of the following criteria were met during a universal screening with 75-g oral glucose tolerance test (oGTT): FPG ≥5.1 mmol/l, 1-h glucose ≥10.0 mmol/l, or 2-h glucose ≥8.5 mmol/l at 24-28 weeks GA, in accordance with the IADPSG and the ADA guidelines (7,8). In total, 1185 women were diagnosed with cGDM. For logistic reasons in a clinical context, a few women were diagnosed outside the 24-28 weeks GA. This included 2.8% (33/1185) diagnosed at 21-23 weeks and 4.6% (55/1185) at 29-31 weeks GA. The criteria for eGDM diagnosis were based on the ADA prediabetes criteria (FPG 5.6-6.9 mmol/l or HbA1c 5.7-6.4%) before 20 weeks GA in women at high-risk for diabetes. High-risk women included those with a history of GDM, obesity (body mass index (BMI) >30 kg/m^2), overweight (BMI ≥25

kg/m^2) and a non-Caucasian origin, first-degree family history of diabetes (mother, father, brother, sister, daughter, son) or polycystic ovarian syndrome (7). Very few women formally reported a confirmed diagnosis of polycystic ovarian syndrome (n=26, 2.1%), which is very likely to be underestimated and because medical charts for this diagnosis were not available for most women, we did not further include it in our analysis. We used this established definition of prediabetes because of the lack of consensus on eGDM screening in the first trimester and based on data that FPG decreases during early pregnancy (12). Furthermore, this is also in line with recent studies (24,27) and other guidelines (28–31). For reasons of simplicity, we refer to them as eGDM, although, strictly speaking, the prediabetes criteria are not a universally acknowledged definition of GDM in early pregnancy. In view of the evolving knowledge, this approach and precise criteria for high-risk were applied less systematically before 2018. From September 2018 onwards, we implemented this in a systematic way for women followed in our obstetric clinic and also retested women diagnosed with eGDM at 20-32 weeks GA using the IADPSG and ADA guidelines that were used to diagnose cGDM (7,8). Based on these criteria, we included and followed up 76 women with eGDM (of which 46 presented after September 2018).

We followed-up women with eGDM and cGDM clinically according to the current guidelines of the ADA and the Endocrine Society (7,32). They had both continuous regular appointments every 1-3 weeks with a medical doctor, a diabetes-specialist nurse and/or a dietician after the GDM diagnosis. During these routine visits, women received information on GDM, specific recommendations regarding lifestyle changes and gestational weight gain based on the 2009 recommendations of the Institute of Medicine (33). Physical activity was encouraged and counselling with a physiotherapist and/or participation in GDM physical activity groups was proposed. Thus, we placed a strong focus on lifestyle and behavioral changes. Women were also

taught how to perform capillary blood glucose testing and were required to perform 4 times per day self-monitoring of blood glucose according to international (7,32) and local guidelines (Vaud Cantonal Diabetes Program) (34) including fasting capillary blood glucose in the morning and 2-h (or 1-h) postprandial blood glucose after each meal. For eGDM, capillary glucose was measured 4x/day for two days per week until the 24th week of GA, when it was then performed daily. Treatment with insulin, or rarely with metformin was introduced when glucose values remained above targets between two or more times during a 1 to 2-week period (FPG >5.3 mmol/l, 1-h postprandial glucose >8 mmol/l and 2-h postprandial glucose >7 mmol/l) despite lifestyle changes according to Swiss guidelines (34). Treatment choice (insulin or metformin) was recommended based on glucose values (i.e., insulin in case of higher values), patient characteristics (i.e., BMI), patient medical history, preference and the fact that metformin can cross the placenta and potentially have a long-term impact on the offspring (35). We introduced and adapted short acting insulin analogues to achieve 1-h postprandial glucose ≤8 mmol/l or 2-h post- prandial glucose ≤7 mmol/l, and long acting insulin analogues to achieve FPG ≤5.3 mmol/l when necessary. Except in the presence of high glycemic values (i.e. HbA1c > 6%), treatment was only initiated after 24 weeks of GA, the timing where interventions show clear benefits (12). The 6-8 weeks postpartum visit included an assessment of the metabolic and medical situation and counseling on lifestyle changes based on cardio-metabolic laboratory results.

Measures

Sociodemographic and anthropometric variables

We collected information on maternal socio-demographic characteristics during a structured face-to-face interview at the first GDM clinic visit. This included age, nationality/ethnic origin

(Switzerland, Europe or North America, Africa, Asia/Western pacific, Latin America and others) and educational level (no formal education, compulsory school achieved, general and vocational training levels, high school and university). Information on previous history of GDM (yes/no), family history of diabetes (yes/no), gravida (one, two and ≥ three), parity (none, one, two and ≥ three), and social support during pregnancy (yes/no) were taken from participants' medical charts. Pre-pregnancy weight was extracted from participants' medical charts or, if missing, was self-reported. We measured height and weight at the first and last GDM visit, and at 6-8 weeks postpartum to the nearest 0.1 cm and 0.1 kg, respectively, with regularly calibrated electronic scales (Seca®). BMI was expressed as a ratio of weight in kilograms to the square of height in meters (kg/m^2).

Obstetric and neonatal outcomes

We assessed adverse obstetric outcomes including gestational hypertension (yes/no), pre-eclampsia (yes/no), GA at delivery (weeks) and preterm delivery (<37 GA; yes/no), as well as caesarean delivery (yes/no). Neonatal adverse outcomes included macrosomia (birthweight ≥4000 g), large-for-gestational-age (LGA) and small-for-gestational-age (SGA) infants were defined as sex-and gestational age–specific birth weight >90th and <10th centile, respectively, according to the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) guidelines (36).

Metabolic and cardiovascular health outcomes

HbA1c was measured using a chemical photometric method (conjugation with boronate; Afinion®) at the first GDM visit and with a High Performance Liquid Chromatography method (HPLC) at 6-8 weeks postpartum, according to international guidelines (37). The chemical

photometric method (Afinion® analyzer) has similar accuracy and precision with HPLC (38). We performed a 75-g oGTT at 6-8 weeks postpartum to measure FPG and 2-hr glucose. At 6-8 weeks postpartum, we defined prediabetes (FPG 5.6-6.9 mmol/l or HbA1c 5.7-6.4% or 2-h plasma glucose 7.8-11.0 mmol/l) and diabetes (FPG ≥7.0 mmol/l, 2-hr glucose ≥11.1 mmol/l or HbA1c ≥6.5%) according to the ADA criteria (7).

We extracted data on the need for glucose-lowering medical treatment during pregnancy (use of insulin and/or metformin; yes/no) from maternal medical records. Gestational weight gain (GWG) was defined as the difference in weight between the end of pregnancy and before pregnancy. Excessive GWG was calculated according to the Institute of Medicine 2009 GWG recommendations based on pre-pregnancy BMI (33). We defined weight retention as the difference in weight at 6-8 weeks postpartum and before pregnancy and waist circumference was measured with a tape measure (calibrated in centimeters). At 6-8 weeks postpartum, we assessed fasting blood lipids including total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and triglycerides. Metabolic syndrome (MetS) was defined according to the International Diabetes Federation guidelines, which is based on either waist circumference >80 cm or BMI ≥30 kg/m^2 and at least two of the following cut-offs: triglycerides ≥1.7 mmol/l, HDL <1.3 mmol/l, blood pressure ≥130/85 mmHg, FPG ≥5.6 mmol/l or type 2 diabetes mellitus (39).

Mental health outcomes

We assessed maternal mental health outcomes including maternal depressive symptoms, well-being and intuitive eating at the first GDM presentation and at 6-8 weeks postpartum in women with eGDM and cGDM. For women with eGDM, we additionally assessed them at 20-32 weeks GA when they were retested for GDM. To measure maternal depressive symptoms, we used the

Edinburgh Postnatal Depression Scale (EPDS). This is a ten-item self-report questionnaire designed and validated to screen women for symptoms of depression in the perinatal period (40). The possible scores of the EPDS range from 0-30 points, with a higher total score indicating more severe depressive symptoms. Maternal well-being was assessed with the WHO-Five Well-Being Index (41). This validated 5-item self-report questionnaire is widely used in endocrinology studies. The items are measured on a 5-point Likert scale ranging from 0 '*at no time*' to 5 '*all of the time*'. The total score from the 5-item is then multiplied by 4 to obtain the final score. Possible scores range from 0-100, with higher scores reflecting higher well-being status. We assessed intuitive eating with a 14-item self-report questionnaire consisting of "eating for physical rather than emotional reasons" (EPR, 8 items) and the "reliance on hunger and satiety cues" (RHSC, 6 items) subscales of the French Intuitive Eating Scale-2 (IES-2) (42). Detailed explanations of how the IES-2 questionnaire was adapted and used in this cohort can be found elsewhere (25,26). The possible scores of IES-2 range between 1 and 5. A higher score of the EPR subscale reflects eating as an answer to hunger and a lower score means eating to cope with emotional distress, whereas a higher score of the RHSC subscale signifies trust in internal cues, and a lower score reflects less ability to regulate food intake.

Statistical analysis

We performed all statistical analyses with Stata/SE 15.1 (StataCorp LLC, TX, USA) (43). Demographic and other descriptive variables were presented as means (±standard deviation) or percentages (%) where appropriate (Table 1). All outcome variables (obstetric and neonatal, metabolic and cardiovascular health, and mental health variables) were normally distributed. We used ANOVA (continuous variables) and Chi-square (categorical variables) tests to determine and compare the differences in obstetric and neonatal outcomes (Table 2), maternal metabolic

and cardiovascular health outcomes (Table 3) and mental health outcomes (Table 4) during pregnancy and at 6-8 weeks postpartum, according to the timing of GDM diagnosis (eGDM *vs* cGDM). We also conducted a multivariable logistic regression analysis using GDM category (eGDM *vs* cGDM) as the predictor and significant outcomes including LGA, need for glucose-lowering medication, prediabetes, diabetes and MetS as outcome variables. We adjusted for the five known risk factors (RF) for GDM and diabetes, including pre-pregnancy BMI, family history of diabetes, history of GDM, ethnicity and GWG as an additional important diabetes-RF in different regression models (Table 5). We did this to evaluate if these RF could explain the differences in outcomes. We adjusted for pre-pregnancy BMI in model 1, GWG in model 2, history of GDM in model 3, family history of diabetes in model 4 and nationality/ethnic origin in model 5. In the 6th model, we adjusted for all 5 RF (Table 5 for all models). In an additional step, we adjusted for surrogate markers of insulin resistance, namely triglycerides and HDL in the postpartum period (results not shown; not done for MetS, as both factors are part of its definition) together with Model 6 (adjustment for all 5 RF). In a supplementary analysis (done as a sensitivity analysis) (44), we focused on the 46 women that presented after September 2018 in whom early screening was done in a very systematic way. In these 46 women, we used a paired t-test to determine and compared the changes in metabolic, cardiovascular, and mental health variables between the early GDM diagnosis visit in the first trimester and GDM confirmation visit at 20-32 weeks GA (44). All statistical significances were two sided and accepted at $p<0.05$.

Results

In total, 76 women (6%) were diagnosed with eGDM (<20 weeks GA) and 1185 (94%) with cGDM (24-28 weeks GA). Mean age was 33±5.7 years and gestational age at GDM diagnosis was 18.9±5.8 and 29.1±2.8 weeks for the eGDM and cGDM respectively (Table 1).

Obstetric and neonatal outcomes

There were no differences in gestational hypertension and pre-eclampsia, mean gestational weeks at delivery, rate of preterm delivery and cesarean section between eGDM and cGDM (all p ≥0.19; Table 2). In this treated cohort, birth weight and the rate of SGA were similar. However, there was a higher proportion of infants with LGA (p=0.028) and a tendency for higher rate of macrosomia (p=0.08) in women with eGDM. The differences in LGA remained significant after adjusting for all five GDM/diabetes-RFs.

Metabolic and cardiovascular outcomes

Per definition, women with eGDM presented with higher mean pre-pregnancy BMI (p<0.001) (Table 3a). Similarly, their FPG at diagnosis and HbA1c at the first GDM visit were higher (both p<0.001). Total GWG was 2 kg less in eGDM (p=0.03), but excess GWG was similar to cGDM. The need for glucose-lowering medical treatment was greater in women with eGDM than in cGDM (p<0.001); this was irrespective of GDM/diabetes-RFs (p≤0.003). Specifically, 62% (n=39) and 18% (n=11) of women with eGDM received insulin and metformin respectively, compared to 40% (n=407) and 9% (n=87) in the cGDM women. In the early postpartum period, there was a tendency for less weight retention (2.9 *vs* 4.4 kg, p=0.06) in eGDM (Table 3b). FPG, 2-hr glucose after oGTT and HbA1c were higher in eGDM compared to cGDM (all p<0.001). The prevalence of prediabetes was 3.1-times higher (47.5% *vs* 15.3%, p<0.001) and diabetes was 7.4-times higher (11.9% *vs* 1.6%, p<0.001) in eGDM compared to cGDM. Regarding lipids, HDL levels were lower, whereas triglycerides levels were higher in eGDM (p≤0.001), but LDL and total cholesterol did not differ. Compared to cGDM, the prevalence of MetS-WC and MetS-BMI were 1.9-times and 1.8-times higher respectively in eGDM (MetS-WC: 62% *vs* 34%, MetS-BMI: 46% *vs* 23%, both p<0.001). The significant differences in the prevalence of prediabetes,

diabetes, MetS-WC, and MetS-BMI were independent of the five GDM/diabetes-RFs (Table 5). When we further adjusted for triglycerides and HDL together with the five RFs, significant differences in LGA, prediabetes and diabetes remained ($p \leq 0.034$, data not shown).

Mental health outcomes

Table 4 shows the mental health outcomes during pregnancy (Table 4a) and at 6-8 weeks postpartum (Table 4b) according to the timing of GDM diagnosis. There were no significant differences in maternal well-being, depression or intuitive eating scores in women with eGDM and cGDM, either at the first GDM visit or in the early postpartum (all $p \geq 0.16$).

Changes in metabolic, cardiovascular and mental health variables

We showed the course of 46 women presenting after 2018 who had early pregnancy clinical follow-up and were retested at 20-32 weeks GA (44). Of those, 90.4% (n=38/42; four (4) were lost to follow-up) had their GDM diagnosis confirmed according to the IADPSG and ADA criteria. In these 42 women, FPG and HbA1c decreased between early diagnosis and GDM confirmation visits (both $p \leq 0.01$) but mental health parameters did not change. HbA1c and FPG decreased in the 38 women whose GDM diagnosis was confirmed ($p < 0.005$). We also compared the sub-group of eGDM (n=38) and cGDM (n=1215) that presented after 2018 (44).

Discussion

This clinical cohort of women with GDM the most important findings were that despite initiating an earlier clinical follow-up focused on lifestyle changes and in spite of a lower GWG and weight retention, women with eGDM had a substantially higher risk of adverse metabolic and cardiovascular outcomes in the postpartum period compared to cGDM. Indeed, the risks for

prediabetes, diabetes and MetS were increased by 2-7-fold. This highly increased risk remained practically unchanged after adjusting for GDM-and-diabetes-RFs that constitute the rationale for early GDM screening in many guidelines. On the other hand, although women with eGDM represented a high-risk group, adverse obstetric and neonatal outcomes were not elevated in this cohort, except for an increased risk of LGA. Despite the strong link between metabolic and mental health in GDM (45), mental health outcomes including depression, well-being and eating behavior during and after pregnancy did not differ.

Early GDM detection and lifestyle counseling in high-risk women provide several additional weeks of medical care to reduce adverse obstetric, neonatal, mental health, metabolic and cardiovascular outcomes. To our knowledge, this study is the first to compare all these outcomes, particularly cardiovascular outcomes between eGDM and cGDM and provides a comprehensive focus on the postpartum: a period where women with GDM have increased cardiovascular risk.

Indeed, the increased need for glucose-lowering medication observed in eGDM compared to cGDM is consistent with a previous meta-analysis (16) and may be explained by their poor metabolic profile (9), greater insulin resistance (46) and prior glycaemia exposure that characterized eGDM. We found a 3-fold increased prevalence of prediabetes and a 7-fold increased prevalence of diabetes in the early postpartum in eGDM compared to cGDM, despite the benefits of early detection, lifestyle intervention and treatment. This suggests that women with eGDM and RFs already have pre-existing impaired glucose tolerance before pregnancy (47,48). It has also been suggested that (pre-existing) dysregulation of cytokines and the increase in free fatty acids in GDM promotes metabolic dysfunction, which might be more pronounced in eGDM (49). In our cohort, women diagnosed with eGDM did not only have a higher FPG, but

also higher HbA1c values at baseline than those diagnosed with cGDM. Our results are in line with a report from the DALI lifestyle study in early pregnancy that observed a higher adverse metabolic profile (with particularly increased insulin resistance) at baseline in women with eGDM compared to those with cGDM (50). These findings are also consistent with the pre-existing baseline dysglycemia suggested in eGDM. Two retrospective studies (22,24) showed higher prevalence of prediabetes in eGDM, whereas one found no differences (23). The prevalence of prediabetes in these studies is slightly lower than the one of our cohort (24-39% in previous studies *vs* 47% in our study). However, the timing of postpartum glucose testing and the distinct identification of prediabetes in these studies differed compared our study.

Beyond glycaemia, we also found a 2-fold increased risk of the MetS and of dyslipidemia in eGDM compared to cGDM, and this, as early as two months postpartum. This may be due to a pre-existing adverse cardiometabolic risk profile in eGDM (47,48). Mechanisms including other cardiovascular determinants that preexisted before pregnancy and pre-eclampsia in pregnancy could also contribute (5). The increased cardiovascular risk in our study was present despite lower gestational weight gain and a tendency for reduced weight retention. It remained increased when we adjusted for classical diabetes or GDM-RF indicating that cardiovascular outcomes observed in eGDM were beyond the impact of these risk factors. The fact that we only screened women with RFs in early pregnancy and our cut-offs for eGDM were above the initially suggested FPG of 5.1 mmol/l probably contributed to these findings. Despite this and in view of the recent findings regarding the increased risk for cardiovascular outcomes and of coronary calcifications, both independent of the development of prediabetes or diabetes in the postpartum (5,6), our findings are very relevant and calls for an earlier and broader intervention in these women.

Mental health outcomes including well-being, depression, and intuitive eating scores were not different between eGDM and cGDM, neither at baseline before lifestyle coaching and clinical follow-up, nor in the postpartum period. Despite the known relationship between mental health and metabolic health in GDM or diabetes, the increased adverse cardiometabolic profile in eGDM in our study was not related to differences in mental health.

In this clinical setting of early diagnosis, lifestyle intervention and medical care, adverse obstetric and neonatal outcomes in these high-risk women with eGDM were not higher than those with cGDM. The only exceptions were LGA and macrosomia. Studies have shown that women with eGDM have more frequent adverse obstetric and neonatal outcomes (12,13) when early screening is performed in high-risk women, as our study. This is particularly the case when higher diagnostic glycemic cut-offs than those initially proposed by the IADPSG are used (8). In that context, our findings could represent the success of early care. The increased maternal adiposity and existing baseline dysglycemia in our eGDM population could explain the increased risk of LGA and macrosomia. Some studies especially those performing universal, and not risk-based, early screening and using lower glycemic cut-offs for diagnosis even showed improvements in obstetrical and neonatal outcomes when women are screened early (12). However, using lower diagnostic criteria for eGDM could lead to an over-diagnosis of women. Using the IADPSG criteria of FPG 5.1 mmol/l was predictive of later GDM, but only 30-50% of these women turned out to have cGDM later on. Using the ADA prediabetes criteria, we observed in a sub-group of women who were retested that 90% (38/42) of women diagnosed with eGDM had their GDM diagnosis confirmed at 20-32 weeks GA, despite a focus on lifestyle adaptations. This suggests that overdiagnosis of eGDM and subsequent over-medicalization and over-treatment may not be major concern using these criteria for these women. The advantage of these criteria is that they

join known criteria outside of pregnancy and that they facilitate interdisciplinary care beyond pregnancy. Other criteria close to the ones used for prediabetes have also been suggested, including FPG ≥5.5 mmol/l or HbA1c of ≥5.9% (12,13,51), but different criteria are yet to be tested in large RCTs (52).

The strengths of our study include the prospective design and the use of well-defined and established criteria (ADA prediabetes criteria) to define eGDM in high-risk women, although there is no consensus on eGDM definition and the initially proposed IADPSG criteria seem to overdiagnose women (8,12,13). To our knowledge, this is the first study to characterize metabolic, cardiovascular, and mental health outcomes between eGDM and cGDM, with a comprehensive focus on the postpartum. The high follow-up rate of 86% in the postpartum and the multiethnic nature of our cohort make our results more generalizable. The prospective data in the postpartum period regarding metabolic, cardiovascular and mental health are new and have an innovative and clinically relevant aspect. They can influence the clinical management of early GDM, especially in the postpartum period. Despite these strengths, this study has limitations. Although we used well-defined criteria to diagnose eGDM and defined high-risk women for early screening, we did this less systematically before September 2018. Also, all the risk factors were possibly not always investigated in women referred from private obstetricians and thus some of them would not have had an early screening. Furthermore, eligible women did not always agree to an early screening. This suggests that some potential high-risk women were not screened early in pregnancy and were categorized as cGDM. The lack of differences in almost all obstetric and neonatal outcomes should be interpreted with caution in view of the small differences in effect sizes and the related statistical power. However, a matched case-control analysis of the 76 cases of eGDM with cGDM would not be beneficial and might represent a bias in itself. This might

have attenuated some differences in outcomes (e.g., obstetrical), but differences in metabolic and cardiovascular outcomes would have been even larger. When we also compared women diagnosed with eGDM and cGDM before and after 2018, the patient characteristics and differences were similar. We did not include additional neonatal data because many variables were missing, and to keep the paper more focused.

Conclusions

To our knowledge, this multiethnic clinical cohort is the first to compare cardiovascular, metabolic and mental health outcomes in women with eGDM and cGDM with a focus on the postpartum. Using the ADA prediabetes criteria for early GDM diagnosis did not lead to an overdiagnosis or overtreatment of eGDM. Women with eGDM benefited from early detection and lifestyle changes and had a lower GWG and weight retention compared with cGDM. Adverse obstetric and neonatal outcomes associated with this high-risk eGDM population were not increased in our cohort, except for LGA. Furthermore, mental health outcomes did not differ. However, during pregnancy, they had higher glycemic values and needed frequent medical treatment. These women had a more atherogenic lipid profile and a 2-7-fold increased prevalence of MetS, prediabetes, and diabetes compared to cGDM. These increased risks remained unchanged when we adjusted for GDM-and-diabetes-RFs. Our results raise concern and suggest a need for systematic metabolic and cardiovascular risk identification and treatment before pregnancy and in the postpartum in these young, but high-risk women as long-term studies have shown an increased risk for cardiovascular diseases in GDM in general, even in the absence of diabetes.

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Data availability

Data generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Figure Legend

Fig 1. Flow chart of study participants

GDM denotes gestational diabetes mellitus. pp denotes postpartum. eGDM (=early GDM) denotes women diagnosed at <20 weeks GA using ADA criteria for prediabetes; cGDM (=classical GDM) denotes women diagnosed at >20 weeks GA using the IADPSG and ADA criteria for GDM (75-g oGTT: FPG ≥5.1 mmol/l, 1-hr glucose ≥10.0 mmol/L or 2-hr glucose ≥8.5 mmol/l).

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Tables and Captions

Table1: Sociodemographic characteristics of participants according to the timing of GDM diagnosis

	GDM diagnosis*		
	eGDM	**cGDM**	
	<20 GA (n=76)	**>20 GA (n=1185)**	
Variable	**N (%)**	**N (%)**	**P-value**
Age (years), *Mean (SD)*	34.05 (5.66)	32.84 (5.74)	0.082
GA at first GDM visit (weeks), *Mean (SD)*	18.93 (5.81)	29.14 (2.79)	**<0.001**
Nationality/ethnic origin			
Switzerland	17 (22.4)	334 (28.3)	**0.003**
Rest of Europe + North America	16 (21.1)	414 (35.1)	
Africa	17 (22.4)	191 (16.2)	
Asia + Oceania	20 (26.3)	154 (13.0)	
Latin America	2 (2.6)	57 (4.8)	
Others	4 (5.3)	31 (2.6)	
Educational level[1]			
No formal education	0 (0.0)	6 (1.1)	0.145
Compulsory school achieved	13 (37.1)	114 (20.1)	
High school	4 (11.4)	59 (10.4)	
General and vocational education	5 (14.3)	143 (25.2)	
University	13 (37.1)	245 (43.2)	
Family history of diabetes[2]			
Yes	35 (46.1)	370 (31.2)	**0.001**
No	41 (53.9)	815 (68.7)	
History of previous GDM[3]			
Yes	38 (50.0)	65 (5.5)	**<0.001**
No	38 (50.0)	1120 (94.5)	
History of macrosomia[3]			
Yes	42 (85.7)	77 (12.5)	**0.002**
No	7 (14.3)	541 (87.5)	
Gravida			
1	24 (31.6)	383 (32.3)	0.974
2	20 (26.3)	319 (26.9)	
≥ 3	32 (42.1)	483 (40.8)	
Parity[4]			
0	35 (46.1)	541 (45.7)	0.746
1	20 (26.3)	371 (31.3)	
2	13 (17.1)	167 (14.1)	
≥3	8 (10.5)	106 (8.9)	
Social support during pregnancy			
Yes	65 (85.5)	1010 (85.2)	0.940
No	11 (14.5)	175 (4.8)	

GDM denotes gestational diabetes mellitus; GA denotes gestational age in weeks; SD denotes standard deviation,
*eGDM (=early GDM) denotes women diagnosed at <20 weeks GA using ADA criteria for prediabetes; cGDM (=classical GDM) denotes women diagnosed at >20 weeks GA using the IADPSG and ADA criteria for GDM (75-g oGTT: FPG ≥5.1 mmol/l, 1-hr glucose ≥10.0 mmol/L or 2-hr glucose ≥8.5 mmol/l)
[1]41 women with eGDM and 618 women with cGDM had missing data on education
[2]Family history of diabetes consists of those with first-degree relationship of the participant (e.g. mother, father, brother, sister, daughter, son)
[3]only for women who had a previous pregnancy
[4]7.8% women who were multiparous had previous history of GDM
All values are expressed as % or as indicated. Chi-square test was used for categorical variables and ANOVA for continuous variables. Bold p values are significant

Table 2: Obstetric and neonatal outcomes according to the timing of GDM diagnosis

	GDM diagnosis*		
	eGDM	**cGDM**	
	<20 GA (n=76)	**>20 GA (n=1185)**	
Variable	**Mean±SD**	**Mean±SD**	**P-value**
Gestational hypertension (yes) (n, %)	2 (2.6)	22 (1.9)	0.312
Pre-eclampsia (yes) (n, %)	1 (1.3)	21 (1.8)	0.173
Gestational age at delivery (weeks)	38.91±5.08	38.68±4.55	0.690
Prematurity, yes (%)[1]	6 (7.8)	103 (8.7)	0.866
Caesarean delivery (yes) (n, %)	31 (40.8)	398 (33.6)	0.199
Birth weight (g)	3168.3±789	3212.7±638	0.589
Macrosomia (yes) (%)[2]	9 (11.8)	87 (7.3)	0.085
LGA, yes (%)	16 (25.0)	153 (14.8)	**0.028**
SGA, yes (%)	12 (15.8)	145 (12.2)	0.296
NICU admission, yes (%)[3]	5 (6.5)	111 (9.36)	0.323

GDM denotes gestational diabetes mellitus; GA denotes gestational age in weeks; LGA denotes large for gestational age; SGA denotes small for gestational age

*eGDM (=early GDM) denotes women diagnosed at <20 weeks GA using ADA criteria for prediabetes; cGDM (=classical GDM) denotes women diagnosed at >20 weeks GA using the IADPSG and ADA criteria for GDM (75-g oGTT: FPG ≥5.1 mmol/l, 1-hr glucose ≥10.0 mmol/L or 2-hr glucose ≥8.5 mmol/l)

[1]Prematurity defined at infant delivery <37 gestational age

[2]Macrosomia defined as birthweight ≥4000g

[3]NICU denotes, Neonatal Intensive Care Unit admissions

All values are expressed as mean and standard deviation unless otherwise stated.

P value derived from ANOVA test for continuous variables and Chi-square test for categorical variables. Bold p values are significant

Table 3: Maternal metabolic and cardiovascular health outcomes during pregnancy and at 6-8 weeks postpartum according to the timing of GDM diagnosis

	GDM diagnosis*		
	eGDM	cGDM	
	<20 GA (n=76)	>20 GA (n=1185)	
Variable	**Mean±SD**	**Mean±SD**	**P-value**
Before and during pregnancy			
Pre-pregnancy weight (kg)	78.32±17.74	69.35±15.68	**<0.001**
Pre-pregnancy BMI (Kg/m^2)	29.78±6.59	25.92±5.56	**<0.001**
Weight at the first GDM visit	82.98±17.30	79.78±15.54	0.097
Fasting glucose at diagnosis (mmol/l)	5.62±0.83	5.13±0.73	**<0.001**
HbA1c at the first GDM visit (%)	5.64±0.55	5.38±0.39	**<0.001**
Need for glucose-lowering treatment (yes) (n, %)	50 (65.8)	494 (41.7%)	**<0.001**
At the end of pregnancy			
Gestational weight gain (kg)	10.73±6.17	12.65±6.43	**0.029**
Excess gestational weight gain (kg)	2.67±0.48	2.50±0.51	0.215
HbA1c at the end of pregnancy (%)	5.64±0.38	5.41±0.38	**<0.001**
At 6-8 weeks postpartum			
Weight (kg)	81.25±16.40	73.78±15.08	**<0.001**
BMI (kg/m^2)	30.84±5.99	27.66±5.36	**<0.001**
Weight retention (kg)	2.87±5.8	4.40±5.97	0.060
Fasting glucose (mmol/l)	5.70±0.87	5.0±0.52	**<0.001**
2-hr glucose after OGTT (mmol/l)	6.53±1.91	5.51±1.64	**<0.001**
HbA1c (%)	5.63±0.59	5.31±0.39	**<0.001**
Prediabetes (yes) (n, %)	28 (47.5)	156 (15.3)	**<0.001**
Diabetes (yes) (n, %)	7 (11.9)	16 (1.6)	**<0.001**
Total cholesterol (mmol/l)	5.26±0.96	5.15±0.96	0.432
HDL (mmol/l)	1.31±0.32	1.51±0.42	**0.001**
LDL (mmol/l)	3.18±0.77	3.09±0.85	0.416
Triglycerides (mmol/l)	1.81±1.38	1.26±0.74	**<0.001**
SBP (mmHg)	112.91±15.05	112.97±12.68	0.972
DBP (mmHg)	73.61±9.93	73.32±9.84	0.833
Metabolic Syndrome (n, %)			
Waist circumference-defined	47 (61.8)	404 (34.1)	**<0.001**
BMI-defined	35 (46.1)	281 (23.7)	**<0.001**

GDM denotes gestational diabetes mellitus; GA denotes gestational age in weeks; HbA1c denotes glycated hemoglobin; SBP denotes systolic blood pressure; DBP denotes diastolic blood pressure; BMI denotes body mass index; OGTT denotes 75g oral glucose tolerance test; HDL denotes high-density lipoproteins; LDL denotes low-density lipoproteins

*eGDM (=early GDM) denotes women diagnosed at <20 weeks GA using ADA criteria for prediabetes; cGDM (=classical GDM) denotes women diagnosed at >20 weeks GA using the IADPSG and ADA criteria for GDM (75-g oGTT: FPG ≥5.1 mmol/l, 1-hr glucose ≥10.0 mmol/L or 2-hr glucose ≥8.5 mmol/l). All values are expressed as mean and standard deviation unless otherwise stated. P value derived from ANOVA test for continuous variables and Chi-square test for categorical variables. Bold p values are significant

Table 4: Maternal mental health outcomes during pregnancy and at 6-8 weeks postpartum according to the timing of GDM diagnosis

	GDM diagnosis*		
	eGDM	cGDM	
	<20 GA (n=76)	>20 GA (n=1185)	
Variable	**Mean±SD**	**Mean±SD**	**P-value**
During pregnancy			
Well-being score at first GDM visit[1]	63.78±18.22	59.96±19.77	0.418
EPDS score at first GDM visit[2]	7.50±4.58	7.00±5.09	0.668
EPR score at first GDM visit[3]	3.76±0.79	3.85±0.86	0.685
RHSC score at first GDM visit[4]	3.40±1.01	3.58±0.86	0.400
At 6-8 weeks postpartum			
Well-being score at 6-8 weeks postpartum[1]	60.50±18.86	65.34±19.02	0.161
EPDS score at 6-8 weeks postpartum[2]	7.29±3.71	5.87±5.00	0.205
EPR score at 6-8 weeks postpartum[3]	2.88±0.1	3.97±0.92	0.242
RHSC score at 6-8 weeks postpartum[4]	3.13±0.1	3.69±0.80	0.489

GDM denotes gestational diabetes mellitus; GA denotes gestational age in weeks

*eGDM (=early GDM) denotes women diagnosed at <20 weeks GA using ADA criteria for prediabetes; cGDM (=classical GDM) denotes women diagnosed at >20 weeks GA using the IADPSG and ADA criteria for GDM (75-g oGTT: FPG ≥5.1 mmol/l, 1-hr glucose ≥10.0 mmol/L or 2-hr glucose ≥8.5 mmol/l)

[1]The World Health Organization-Five Well-Being Index (WHO-5)

[2]EPDS denotes Edinburg postnatal depression scale

[3]EPR denotes eating for physical rather than emotions subscale of the intuitive eating scale-2 (IES-2)

[4]RHSC denotes reliance on hunger and satiety cues subscale of the intuitive eating scale-2 (IES-2)

All values are expressed as mean and standard deviation. P value derived from ANOVA test. Bold p values are significant

Table 5: Associations between the timing of GDM diagnosis and significant neonatal, maternal metabolic and cardiovascular outcomes when adjusting for risk factors of diabetes

Variable	Model RF1		Model RF2		Model RF3		Model RF4		Model RF5		Model all RF	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Neonatal outcomes												
LGA	1.9 (1.1-3.6)	**0.027**	2.4 (1.3-4.5)	**0.007**	1.7 (0.9-3.2)	0.126	1.9 (1.1-3.6)	**0.023**	1.9 (1.1-3.5)	**0.028**	2.3 (1.1-4.6)	**0.021**
Maternal outcomes during pregnancy												
Medication*	2.4 (1.4-4.0)	**0.001**	4.2 (2.3-8.0)	**<0.001**	2.2 (1.3-3.7)	**0.003**	2.5 (1.5-4.1)	**<0.001**	2.5 (1.6-4.2)	**<0.001**	3.2 (1.6-6.4)	**0.001**
Maternal metabolic and cardiovascular outcomes in the postpartum												
Prediabetes	5.6 (3.2-9.6)	**<0.001**	6.2 (3.4-11.2)	**<0.001**	5.7 (3.1-10.5)	**<0.001**	6.4 (3.7-11.1)	**<0.001**	6.1 (3.5-10.6)	**<0.001**	4.1 (2.6-9.9)	**0.001**
Diabetes	10.9 (4.0-29.6)	**<0.001**	10.5 (3.7-29.9)	**<0.001**	5.4 (1.7-17.2)	**0.004**	9.2 (3.5-24.0)	**<0.001**	8.4 (3.3-21.7)	**<0.001**	8.2 (2.2-29.9)	**0.001**
MetS-WC	2.5 (1.5-4.1)	**<0.001**	3.5 (2.1-6.2)	**<0.001**	2.9 (1.7-4.9)	**<0.001**	1.8 (1.1-2.2)	**<0.001**	3.2 (1.9-5.1)	**<0.001**	2.8 (1..5-5.2)	**0.001**
MetS-BMI	1.9 (1.2-3.3)	**0.008**	2.7 (1.6-4.8)	**<0.001**	2.5 (1.5-4.2)	**<0.001**	2.7 (1.7-4.4)	**<0.001**	2.9 (1.8-4.8)	**<0.001**	1.9 (1.2-3.5)	**0.041**

RF denotes diabetes risk factor, OR denotes odds ratio, CI denotes confidence interval; LGA denotes large for gestational-age; MetS-WC denotes metabolic syndrome defined by waist circumference; MetS-BMI denotes metabolic syndrome defined by BMI

*Medication denotes need for glucose-lowering treatment during pregnancy

Model RF1: adjusted for pre-pregnancy body mass index

Model RF2: adjusted for gestational weight gain

Model RF3: adjusted for history of gestational diabetes

Model RF4: adjusted for family history of diabetes

Model RF5: adjusted for nationality/ethnic origin

Model all RF: adjusted for pre-pregnancy body mass index, gestational weight gain, history of gestational diabetes, family history of diabetes and nationality/ethnic origin

Bold p values are significant

Figure 1