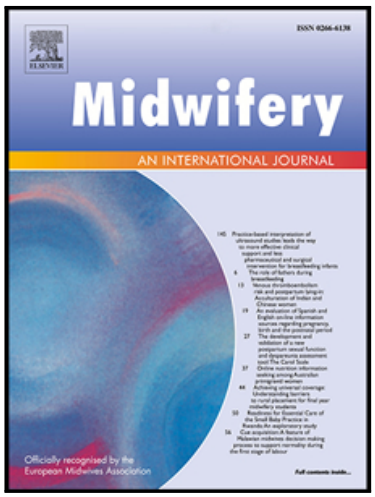

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Comparison of risk factors and pregnancy outcomes of gestational diabetes mellitus diagnosed during early and late pregnancy

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Abstract

Objective: To compare risk factors and pregnancy outcomes of gestational diabetes mellitus (GDM) diagnosed during early and late pregnancy.

Design: Prospective population-based cohort study.

Setting: Community health care centers of "X".

Participants and measurements: 1000 pregnant women who were eligible and consented to participate underwent fasting plasma glucose testing at the first prenatal visit (6-14 weeks). The women free from GDM or overt diabetes were screened at 24-28 weeks of gestation using a 75-g, 2-hour oral glucose tolerance test. The diagnosis of GDM was reached through the International Association of the Diabetes and Pregnancy Study Groups. Early-onset GDM was defined as the diagnosis of GDM at the first prenatal visit. Late-onset GDM was defined as the diagnosis of GDM later at 24-28 weeks.

Findings: Prevalence of GDM was 10% (95% CI: 8.1-11.9) at the first prenatal visit. GDM incidence was 9.3% (95% CI: 7.4-11.2) at 24-28 weeks of gestation. Family history of diabetes, and previous gestational diabetes and maternal age were the independent risk factors for GDM during early and late diagnosis. GDM was associated with increased risk of macrosomia, large for gestational age, and cesarean section in both periods while, neonates of women with early-

onset GDM were more likely to have an apgar score at 1-minute <7, and neonatal respiratory distress syndrome and were more admitted to the neonatal intensive care unit.

Key conclusion and implication for practice: Despite early screening and current practice management, early-onset GDM was associated with poorer pregnancy outcomes compared to the late-onset group. Women with early-onset GDM would benefit from more strict surveillance and management strategies to improve pregnancy outcomes. Further studies are needed to evaluate the efficacy of alternative management approaches in these high risk women.

Keywords

Early screening, Gestational diabetes, Pregnancy outcomes

Introduction

Gestational diabetes mellitus (GDM) is a common condition of glucose intolerance during pregnancy associated with adverse maternal and fetal outcomes (Jain et al., 2014; Meek et al., 2015; Oster et al., 2014). The global burden of GDM varies widely from 1% to 14%, depending on the population studied and diagnostic method used (Ben-Haroush et al., 2003; Hollander et al., 2007). The differences are more evident in studies conducted in "X" where the reported prevalence of the disease varied from 1.3% to 18.6% (Jafari-Shobeiri et al., 2015). Early diagnosis of diabetes might allow earlier intervention, especially for those women at risk and potentially reduces either the later development of GDM or its associated morbidities (Riskin-Mashiah et al., 2009). The strategy of universal screening or screening of high-risk women at the first prenatal visit was initially noted by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (2010). It recommended the use of any available glucose measurement [fasting plasma glucose (FPG), random plasma glucose, or hemoglobin A1C] for initial detection of undiagnosed overt diabetes or GDM and identified that all degrees of hyperglycemia are linked linearly to adverse outcomes in pregnancy, with no obvious inflection point for this risk (Metzger et al., 2008). This has led to considerable difficulty

in defining GDM. In pregnant women, similar to non-pregnant state FPG levels equal or above 126 mg/dl is considered diagnostic for overt diabetes. Women with FPG levels between 92-125 mg/dl are identified with GDM (IADPSG Consensus Panel, 2010). At present, there is a scarcity of evidence regarding the efficacy of the strategy of early identification and treatment of GDM before 24 weeks of gestation. The reason for the identification of dysglycemia early in pregnancy arises from the effect of early maternal hyperglycemia on excessive fetal growth in women with type 1 diabetes (Page et al., 1996; Wong et al., 2002). A study excluded pre-existing diabetes, and reported a relationship between GDM and even milder first trimester FPG and adverse pregnancy outcomes (Riskin-Mashiah et al., 2009). On the other hand, early detection of glucose intolerance reduced the risk of any diabetes-related complications in women with GDM (Bartha et al., 2003). Although, no clinical risks were found to differ between early and late diagnosis of GDM (Bunthalarath et al., 2004), some risk factors and pregnancy outcomes were more likely to occur in women with early diagnosis of GDM (Bartha et al., 2000). The objective of this study was firstly to determine the risk factors associated with GDM diagnosed during early and late pregnancy. Secondly, we aimed to determine the association of early- and late-onset GDM with maternal and neonatal outcomes.

Methods

Subjects

This prospective population-based cohort study was conducted in 10 urban community health care centers located in different areas of "X" with over two million inhabitants. A total of 1000 eligible consecutive pregnant women attending these community health care centers between October 2015 and January 2017 was studied. We enrolled women aged 18-45 years and data from all singleton pregnancies were obtained from prenatal records and/or from the patient

at the first prenatal visit (6-14 weeks) (The Population and Family Health Office, 2016). We obtained the following patients information: demographic information, drug consumption, any anti-diabetic agent use, maternal or paternal family history of diabetes, current pregnancy complications, history of previous pregnancies (e.g., previous diagnosis of GDM, macrosomia, stillbirth, neonatal death, recurrent abortion ≥2, polyhydramnios, eclampsia/preeclampsia, cesarean section, etc.), blood testing, and clinical measurements including weight, height, and systolic and diastolic blood pressure. A 24 h questionnaire was used to assess physical activity of women, which was given to them at their first or second prenatal visit (6-14 or 16-20 weeks). For viable pregnancies, birth records including preterm birth, birthweight, birth height, head circumference, chest circumference, 1 and 5-minutes apgar scores, preeclampsia, gestational hypertension, stillbirth, neonatal death, type of labor [cesarean section and vaginal (natural or instrumental) birth] were obtained from hospital records. Women with known type 1 and type 2 diabetes, non-viable pregnancy (miscarriage), placenta previa, chronic medical condition such as high blood pressure, severe heart disease, liver disease, infections such as HIV and hepatitis, bariatric surgery, any surgery to change the glucose absorption rate, twin pregnancy, and women who were unavailable or incompliant to follow were excluded from the study.

Diagnosis of GDM and management approach

Women were universally screened for overt diabetes and GDM at their first prenatal visit (6-14 weeks) at which FPG was measured. FPG ≥126 mg/dl indicated the presence of overt diabetes. Women with FPG 92-125 mg/dl were considered as early-onset GDM (IADPSG Consensus Panel, 2010). Women without diabetes or GDM in early pregnancy underwent a 75-g, 2-hour oral glucose tolerance test at 24-28 weeks. IADPSG criteria used to diagnose GDM with 75-g, 2-hour oral glucose tolerance test were as follows: FPG ≥92 mg/dl or; 1h plasma glucose

≥180 mg/dl or; 2h plasma glucose ≥153 mg/dl (IADPSG Consensus Panel, 2010). Management of women diagnosed as having GDM in either early or late diagnosis periods did not differ. Women with GDM in both periods received similar therapeutic interventions, including nutrition counseling and lifestyle modification according to the National Protocol for Pregnancy (The Population and Family Health Office, 2016). A dietitian instructed participants about a 3-meal, 2 to 4-snack standard daily meal plan. Caloric restriction was prescribed for obese women based on 25 kcal/kg for actual maternal weight in pregnancy, and 35 kcal/kg for non-obese subjects. Approximately 40% to 45% of calories was derived from carbohydrates. If glycemic control was poor by nutrition counseling and lifestyle modification within two weeks, physicians would consider insulin or oral hypoglycemic agents to treat GDM. Patients were advised to carry out self-monitoring of their blood glucose. The objective for all patients was to reach the same metabolic goals, according to the recommendation from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (Metzger et al., 2007) that is the following targets for maternal capillary glucose concentrations: fasting plasma glucose ≤95 mg/dl and either one-hour post-meal ≤140 mg/dl or two-hour post-meal ≤120 mg/dl.

Definitions

Pre-pregnancy body mass index (BMI) was calculated as a self-reported pre-pregnancy weight of mother divided by height squared (kg/m^2). Physical activity assessment was done using a 24 hour questionnaire (Ainsworth et al., 2000). Women were asked to write every single activity that they do over a 24 hour and time spent on it. Further, we assigned each activity a Metabolic Equivalent of Task score multiplying its time (in hour). The energy expenditure of participants was further calculated by summing the Metabolic Equivalent of Task-hour values. Parity was defined as the number of viable previous pregnancies. Gestational age at the time of

birth was calculated based on the last normal menstrual period or the first trimester ultrasonography. Macrosomia was defined as birthweight >4000 g. Low birthweight was defined as birthweight <2500 g. Preeclampsia was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two or more occasions with proteinuria ≥1+ on dipstick. Preterm birth was defined as birth prior to 37 weeks of gestation. Stillbirth was defined as fetal death after 20 weeks of pregnancy resulting in a baby born without signs of life (The Population and Family Health Office, 2016). Large for gestational age and small for gestational age was defined as gender- and gestational age-specific birthweight >90^{th} centile and <10^{th} centile based on a global reference for birthweight percentiles (Fenton and Kim, 2013).

Statistical analysis

The continuous variables were summarized by mean and standard deviation (SD), the categorical variables were summarized by frequencies. Chi-square or Fisher's exact tests (for categorical variables) and independent-samples t tests (for continuous variables) were used to compare groups. Univariate and multiple logistic regression were used firstly to assess the associations between the potential risk factors and GDM, and secondly, to study the influence of GDM on pregnancy outcomes in both periods. The results of logistic regression are presented as crude and adjusted ORs (95% CIs), which included family history of diabetes, previous GDM, and maternal age as covariates. Data were analyzed using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Reported *P*-values were two-tailed and *P*-values <0.05 were considered to be statistically significant.

Findings

We enrolled 1000 pregnant women who were eligible and consented to participate in the study. Excluding women with known diabetes (n=11), the ones who had a miscarriage (n=18) or

twin pregnancy (n=7), and women who were unable or incompliant to follow the protocol (n=35), a total of 929 patients meeting our inclusion criteria delivered during the study period. GDM was diagnosed in 171 women (18.4%). Ninety-three had the condition diagnosed during early pregnancy (54.4% of women with GDM and 10% of all pregnant women). The other 78 (45.6% of women with GDM and 9.3% of all pregnant women) had normal glucose tolerance during early pregnancy but developed GDM later.

Baseline characteristics and birth outcomes

Of all study women 32.5% (302) were overweight (BMI 25–29.9 kg/m^2), and 10.4% (97) were obese (BMI ≥ 30 kg/m^2). The average (SD) pre-pregnancy BMI was 24.6 (4.2) kg/m^2. The mean (SD) age was 29.2 (4.7) (range 18-44) year. The years of education varied from 0 to 23 years with the mean (SD) of 12.5 (3.6) year. The mean (SD) gestational age at the time of birth was 38.6 (1.5) (ranged 27.7- 42.3) weeks.

Table 1 presents the group means and proportions of baseline maternal characteristics and pregnancy outcomes for women diagnosed as GDM during early and late pregnancy compared to women without GDM. As expected, women with GDM during early and late pregnancy were older, less active, had higher pre-pregnancy BMI, and FPG at the first prenatal visit and higher proportion of family history of diabetes. Compared to women without GDM, women with early-onset GDM had a higher proportion of previous GDM and history of infertility treatment, while women with late-onset GDM had a higher proportion of the earlier cesarean section, pre-existing hypertension, and history of polyhydramnios and neonatal death. Compared to women without GDM, women with late-onset GDM were likely to have gestational hypertension (12.8% vs. 6.1%; P<0.05), mostly because of a higher rate of pre-existing hypertension (6.4% vs 2.2%; P<0.05).

With regard to birth outcomes, a higher birthweight and higher proportions of macrosomia and cesarean section were found in women with GDM during early and late pregnancy. Neonates of women with early-onset GDM had slightly lower apgar scores at 1 and 5-minutes, and higher proportion of neonatal respiratory distress syndrome and were more admitted to the neonatal intensive care unit.

Compared with women in whom GDM was diagnosed at or after 24 weeks of gestation (late-onset GDM), women with early GDM had higher FPG (P <0.001), and were more likely to have a family history of diabetes (P <0.05), previous GDM (P <0.05), neonatal intensive care unit admission (P <0.05), and neonatal respiratory distress syndrome (P <0.05).

Risk factors of early- and late-onset GDM

To determine the association of potential risk factors with GDM, univariate logistic regression was performed (Table 2). Crude odds ratio showed that a family history of diabetes, maternal age >35 years, pre-pregnancy BMI ≥30 kg/m^2, and lower physical activity were significantly associated with both early- and late-onset GDM. While, the risk of early-onset GDM was significantly associated with parity, and higher proportion of previous gestational diabetes and history of infertility treatment, pre-existing hypertension, earlier cesarean section, and history of neonatal death and polyhydramnios significantly increased the risk of late-onset GDM. To examine the independent contribution of the risk factors on the timing of GDM diagnosis, we performed multiple logistic regression. The family history of diabetes was an independent risk factor for both early- and late-onset GDM. Previous gestational diabetes independently increased the risk of early-onset GDM and maternal age >35 years increased the risk of late-onset GDM (Table 2).

Adverse birth outcomes of early- and late-onset GDM

Women with GDM diagnosed in early and late pregnancy were more likely to develop macrosomia, large for gestational age, and cesarean section. The risk associated with early-onset GDM was more pronounced for neonatal outcomes. Early-onset GDM significantly increased the risk of apgar score at 1-minute <7, and neonatal respiratory distress syndrome and neonatal intensive care unit admission. These associations remained significant after adjusting for potential confounders. We found no association of GDM with pregnancy outcomes, including low birthweight, small for gestational age, preeclampsia, gestational hypertension, and preterm birth (Table 3).

Discussion

The present study indicated that the early GDM diagnosis was associated with adverse pregnancy outcomes, including cesarean section, macrosomia, large for gestational age, neonatal intensive care unit admission, neonatal respiratory distress syndrome, and apgar score at 1-minute <7. Our study demonstrates more evidence for the clinical relevance of an early diagnosis of GDM while, debate and discussion still continue in the literature. Although, some studies have demonstrated little evidence to support for early diagnosis of GDM (Zhu et al., 2013), others consider GDM diagnosed in early pregnancy as a risk factor for pregnancy complications and outcomes (Bartha et al., 2003; Riskin-Mashiah et al., 2009). This disparity has also come up with the use of FPG as a proper screening test for early diagnosis of GDM. Although FPG has poor specificity (high false positive rate) which makes it an inefficient screening test for GDM (Sacks et al., 2003), however, universal screening of women with a FPG test seems reasonable due to several advantages and decreases the number of oral glucose tolerance tests needed for the diagnosis of GDM (Agarwal, 2016).

In our study, the GDM prevalence in early pregnancy was 10%, which included more than half of women with gestational diabetes. This figure represents a significant percentage of both the total cases of GDM and the cases in our population compared to other studies (Bartha et al., 2000; Riskin-Mashiah et al., 2009). GDM incidence varied from 1.3% to 18.6% in individual studies performed in "X" with a pooled estimate of 3.4% (Jafari-Shobeiri et al., 2015). The present study indicated an incidence rate of 9.3% for GDM using IADPSG criteria. Clinical risk factors associated with GDM included maternal age, family history of diabetes, and previous GDM. Family history of diabetes was an independent predictor for GDM during both early- and late-onset diagnosis. It has been a strong predictor of GDM in "X" pregnant women (Moosazadeh et al., 2016). Therefore, evaluating pregnant women with a family history of diabetes is already an effective strategy for preventing GDM and its subsequent outcomes.

The first study to evaluate the usefulness of first trimester screening by FPG was done by Riskin-Mashiah et al. (2009). The authors explicitly excluded pre-existing diabetes and found that higher levels of FPG, below than that considered as diabetes, increased the risk of adverse pregnancy outcomes, including macrosomia and/or large for gestational age, and cesarean section. Consistently, GDM independently increased the risk of macrosomia, large for gestational age, and cesarean section in our early-onset group. We also found a positive association of GDM diagnosed during late pregnancy with increased risk of macrosomia, large for gestational age, and cesarean section as previously shown (Keshavarz et al., 2005). Maternal obesity has been a potential risk factor for macrosomia and cesarean deliveries (Hawkins et al., 2008). Our finding of higher pre-pregnancy BMI in women with GDM did not support this claim and was not contributed to the increased risk of macrosomia and large for gestational age, although it was contributed to the increased risk of cesarean section in early- and late-onset GDM, respectively.

Studies have shown that the risk associated with early-onset GDM is more pronounced with neonatal outcomes, including neonatal intensive care unit admission and neonatal respiratory distress syndrome (Sweeting et al., 2016; Vignoles et al., 2011). Consistently, we found an increased risk of the neonatal respiratory distress syndrome after adjusting for potential confounders in mothers with early-onset GDM. All the neonate of mothers with early-onset GDM admitted to the neonatal intensive care unit was among neonatal respiratory distress cases and had an apgar score at 1-minute below 7.

It is possible that early intervention avoids some complications commonly related to GDM (Bartha et al., 2003). However, despite treatment, higher rates of pregnancy complications such as preeclampsia, preterm birth, cesarean section, and neonatal intensive care unit admission were found in women with early-onset GDM, which were comparable to the rates seen in women with pre-existing diabetes (Sweeting et al., 2016). In our study, 48.2 percent of the early diagnosis group required pharmacological agents compared to 24.7 percent of women in whom GDM was diagnosed at or after 24 weeks of gestation. It may reflect a more severe dysglycemia and indicates the significance of plasma glucose levels higher than normal thresholds at the first trimester of pregnancy. Besides, longer duration of the condition for women with early-onset GDM result in poorer pregnancy outcomes in these women, despite early screening and management.

Our study has strengths and limitations. Its strengths include population-based evaluation for GDM. We only included pregnant women from one academic institution in one geographic area. This can be considered as a strength of the study in that pregnancy management was fairly consistent during the study period although, it may also be considered a limitation because our findings do not necessarily generalize to pregnant women in other regions. We also report novel

findings of the incidence rate of GDM in a "real life" clinical setting. There are some other limitations related to this study. While the sample size was believed to be adequate for analysis as a whole, the sample size limited our ability to detect potentially clinically meaningful differences in some pregnancy outcomes between GDM and healthy groups, as judged by a wide 95% CI. The higher rate of cesarean section in our study should be interpreted with caution as it would be partially related to the general tendency of "X" women and that they frequently request elective cesarean section and it also depends upon gynecologist decision. At last, no screening for GDM was performed at 24-28 weeks of gestation in women diagnosed with early-onset GDM, which would be another limitation of the study as some experts (McIntyre et al., 2016) as well as American Diabetes Association (2018) do not support the IADPSG approach to diagnose GDM in early pregnancy.

In conclusion, this study demonstrated that despite early screening and current practice management, early-onset GDM was associated with adverse pregnancy outcomes. Our study supports the IADPSG recommendation regarding early identification of GDM. It is important because women with early-onset GDM had poorer pregnancy outcomes compared to the late-onset group and would benefit from more strict surveillance and management strategies to improve pregnancy outcomes. The encouraging results obtained in this study highlight the need for further studies to confirm these findings and to evaluate the efficacy of alternative management approaches, including life style modifications and pharmaceutical treatments in these high risk women.

Conflict of interest: None declared**.**

Ethical approval: This study was approved by the Isfahan University of Medical Sciences Ethical Committee. All participants gave written informed consent.

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Table 1. Maternal characteristics and pregnancy outcomes of normal pregnancy, and early- and late-onset gestational diabetes mellitus.

Variable	**Normal (n=758)**	**Early-onset GDM (n=93)**	**Late-onset GDM (n=78)**
		% (n)	
Age >35 years	7.4 (56)	14.0 (13)*	21.8 (17)***
Pre-pregnancy BMI ≥30 kg/m^2	8.8 (67)	18.3 (17)**	16.7 (13)*
Parity			
Primiparous	42.5 (322)	44.1 (41)	38.5 (30)
Multiparous	11.5 (87)	18.3 (17)	17.9 (14)
Family history of diabetes	29.6 (224)	60.2 (56)***	43.6 (34)*
Previous gestational diabetes	1.5 (11)	8.6 (8)***	1.3 (1)
Pre-existing hypertension	2.2 (17)	2.2 (2)	6.4 (5)*
History of macrosomia	0.4 (3)	1.1 (1)	1.3 (1)
History of preeclampsia	1.8 (14)	2.2 (2)	5.1 (4)
History of cesarean section	29.0 (220)	36.6 (34)	41.0 (32)*

History of polyhydramnios	0.8 (6)	2.2 (2)	3.8 (3)*
History of stillbirth	0.7 (5)	1.1 (1)	2.6 (2)
History of neonatal death	0.4 (3)	0.0 (0)	2.6 (2)*
History of infertility treatment	7.8 (59)	18.3 (17)**	12.8 (10)
History of recurrent abortion ≥2	2.8 (21)	4.3 (4)	3.8 (3)
History of preterm birth	2.1 (16)	0.0 (0)	3.8 (3)
Education			
Less than high school	6.5 (49)	7.5 (7)	10.4 (8)
High school	55.4 (418)	57.0 (53)	53.2 (41)
College graduate	38.1 (287)	35.5 (33)	36.4 (28)
Macrosomia	1.5 (11)	6.5 (6)**	7.7 (6)***
Low birthweight	6.6 (50)	7.5 (7)	3.8 (3)
Preterm birth	7.1 (54)	11.8 (11)	9 (7)
Cesarean section	53.8 (408)	67.7 (63)*	70.5 (55)**
NICU admission	4.4 (33)	12.9 (12)**	3.8 (3)
Preeclampsia	3.6 (27)	6.5 (6)	6.4 (5)
Gestational hypertension	6.1 (46)	8.6 (8)	12.8 (10)*
Polyhydramnios	0.5 (4)	0.0 (0)	1.3 (1)
NRD syndrome	4.9 (37)	14.0 (13)***	3.8 (3)
Fetal anomalies	0.9 (7)	0.0 (0)	1.3 (1)
Stillbirth	0.3 (2)	0.0 (0)	0.0 (0)
		Mean (SD)	
FPG at first prenatal visit (mg/dl)	82.8 (6.4)	99.9 (6.7)***	85.5 (5.2)***
Systolic BP (mmHg)	102.5 (9.6)	103.2 (10.2)	105.0 (9.8)
Diastolic BP (mmHg)	65.6 (8.6)	66.5 (9.0)	67.1 (8.8)
Physical activity (met-hr/day)	34.9 (6.0)	33.4 (4.8)*	33.2 (4.3)*
Maternal age (years)	28.8 (4.6)	30.7 (4.6)***	31.1 (4.9)***
Pre-pregnancy BMI (kg/m^2)	24.2 (4.1)	26.5 (4.2)***	26.2 (4.7)***
Birthweight (g)	3112.6 (435.2)	3254.1 (540.8)**	3216.8 (465.6)*
Birth height (cm)	49.8 (2.4)	49.9 (2.9)	49.8 (2.2)
Head circumference (cm)	34.6 (1.4)	34.6 (1.6)	34.7 (1.3)
Chest circumference (cm)	33.3 (1.7)	33.6 (2.2)	33.4 (1.8)
Apgar Score (5 min.)	9.93 (0.34)	9.82 (0.46)**	9.86 (0.42)
Apgar Score (1 min.)	8.88 (0.59)	8.60 (0.95)***	8.77 (1.10)
Gestational age at birth (weeks)	38.7 (1.5)	38.5 (1.9)	38.5 (1.3)

*P<0.05, **P<0.01, ***P<0.001 compared with normal group; GDM, gestational diabetes mellitus; BMI, body mass index; NICU, neonatal intensive care unit; NRD, neonatal respiratory distress; FPG, fasting plasma glucose; BP, blood pressure.

Table 2. ORs and 95% CIs for risk factors associated with GDM diagnosed in early and late pregnancy.

Risk factor	Normal	Early-onset GDM	Late-onset GDM
Maternal age >35 (year)			
Crude	1.00	2.0 (1.1-3.9)*	3.5 (1.9-6.4)***
Adjusted	1.00	1.9 (0.9-4.3)	3.4 (1.5-7.5)**
Pre-pregnancy BMI ≥30 (kg/m^2)			
Crude	1.00	2.3 (1.3-4.1) **	2.1 (1.1-3.9)*
Adjusted	1.00	1.8 (0.9-3.7)	1.6 (0.7-3.7)
Parity			
Crude	1.00	1.3 (1.0-1.7)*	1.1 (0.8-1.5)
Adjusted	1.00	0.9 (0.6-1.4)	0.8 (0.5-1.3)
Family history of diabetes			
Crude	1.00	3.6 (2.3-5.6)***	1.8 (1.1-2.9)*
Adjusted	1.00	3.1 (1.9-5.2)***	2.2 (1.2-3.9)*
Previous gestational diabetes			
Crude	1.00	6.4 (2.5-16.3)***	0.9 (0.1-6.9)
Adjusted	1.00	3.2 (1.1-10.3)*	1.1 (0.1-9.0)

Pre-existing hypertension			
Crude	1.00	0.9 (0.2-4.3)	2.9 (1.1-8.3)*
Adjusted	1.00	1.2 (0.2-8.4)	0.9 (0.1-12.7)
History of macrosomia			
Crude	1.00	2.7 (0.3-26.6)	3.3 (0.3-31.8)
Adjusted	1.00	2.1 (0.1-31.8)	2.6 (0.2-39.5)
History of preeclampsia	1.00		
Crude	1.00	1.2 (0.3-5.2)	2.9 (0.9-8.9)
Adjusted		0.7 (0.1-8.4)	3.5 (0.3-48.6)
History of cesarean section			
Crude	1.00	1.4 (0.9-2.2)	1.7 (1.1-2.7)*
Adjusted	1.00	1.5 (0.8-2.6)	1.8 (0.9-3.4)
History of polyhydramnios			
Crude	1.00	2.8 (0.5-13.8)	5.0 (1.2-20.4)*
Adjusted	1.00	2.5 (0.2-28.8)	0.4 (0.03-6.1)
History of stillbirth			
Crude	1.00	1.6 (0.2-14.2)	3.9 (0.8-20.8)
Adjusted	1.00	1.3 (0.1-16.3)	1.7 (0.1-22.9)
History of neonatal death			
Crude	1.00	NA†	6.6 (1.1-40.2)*
Adjusted	1.00	NA	7.3 (0.5-102.1)
History of infertility treatment			
Crude	1.00	2.7 (1.5-4.8)**	1.7 (0.8-3.6)
Adjusted	1.00	1.3 (0.6-2.7)	0.9 (0.3-2.4)
Education ≤12 (year)			
Crude	1.00	1.1 (0.7-1.8)	1.1 (0.7-1.8)
Adjusted	1.00	1.1 (0.6-1.9)	1.3 (0.7-2.5)
Physical activity (met-hr/day)			
Crude	1.00	0.95 (0.91-0.99)*	0.95 (0.89-0.99)*
Adjusted	1.00	0.95 (0.91-1.01)	0.95 (0.89-1.00)

*P<0.05, **P<0.01, ***P<0.001; GDM, gestational diabetes mellitus; BMI, body mass index.
†NA, not analyzed.

Table 3. ORs and 95% CIs for maternal and neonatal outcomes associated with GDM diagnosed in early and late pregnancy.

Outcomes	Normal	Early- onset GDM	Late-onset GDM
Macrosomia (>4000 g)			
Crude	1.00	4.7 (1.7-12.9)**	5.6 (2.1-15.7)**
Adjusted	1.00	4.5 (1.5-13.2)**	4.9 (1.7-14.2)**
Low birthweight (<2500 g)			
Crude	1.00	1.1 (0.5-2.6)	0.6 (0.2-1.8)
Adjusted	1.00	1.0 (0.4-2.3)	0.5 (0.2-1.6)
Cesarean section			
Crude	1.00	1.8 (1.1-2.8)*	2.1 (1.2-3.4)**
Adjusted	1.00	1.7 (1.03-2.6)*	1.8 (1.1-3.1)*
Preeclampsia			
Crude	1.00	1.9 (0.7-4.6)	1.9 (0.7-4.9)
Adjusted	1.00	1.8 (0.7-4.6)	1.5 (0.6-4.3)
Gestational hypertension			
Crude	1.00	1.5 (0.6-3.2)	2.3 (1.1-4.7)*
Adjusted	1.00	1.5 (0.5-3.3)	1.9 (0.9-4.1)
NICU admission			
Crude	1.00	3.2 (1.6-6.5)**	0.9 (0.3-2.9)
Adjusted	1.00	2.6 (1.2-5.4)*	0.7 (0.2-2.5)

Polyhydramnios			
Crude	1.00	NA†	2.4 (0.3-22.2)
Adjusted	1.00	NA	1.8 (0.2-17.8)
NRD syndrome			
Crude	1.00	3.1 (1.6-6.2)**	0.8 (0.2-2.6)
Adjusted	1.00	2.6 (1.3-5.3)**	0.7 (0.2-2.3)
Neonatal Jaundice			
Crude	1.00	0.94 (0.58-1.53)	0.88 (0.52-1.51)
Adjusted	1.00	0.97 (0.59-1.60)	0.85 (0.49-1.45)
LGA			
Crude	1.00	2.3 (1.3-3.9)**	2.5 (1.4-4.5)**
Adjusted	1.00	1.9 (1.1-3.5)*	2.2 (1.2-4.0)**
SGA			
Crude	1.00	0.7 (0.1-5.3)	NA
Adjusted	1.00	0.6 (0.1-5.2)	NA
Preterm birth (<37 weeks)			
Crude	1.00	1.7 (0.9-3.5)	1.3 (0.6-2.9)
Adjusted	1.00	1.4 (0.7-2.8)	0.9 (0.4-2.3)
Apgar score at 1 min.<7			
Crude	1.00	11.2 (4.3-29.3)***	2.4 (0.5-11.8)
Adjusted	1.00	8.0 (2.9-22.1)***	2.2 (0.5-11.2)

*P<0.05, **P<0.01, ***P<0.001; GDM, gestational diabetes mellitus; NICU, neonatal intensive care unit; NRD, neonatal respiratory distress; LGA, large for gestational age; SGA, small for gestational age.
†NA, not analyzed.