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Incidence and risk factors for gestational diabetes mellitus in twin versus singleton pregnancies

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Abstract

Objective To compare the incidence and risk factors for gestational diabetes mellitus (GDM) between women with twin and singleton pregnancies.

Methods Retrospective study of all women who had a twin or singleton birth in Ontario (2012–2016). Risk ratios (RR) and 95% CIs for GDM (stratified by type of treatment) were adjusted for relevant confounding variables. Multivariable Poisson regression analysis was used to identify risk factors for GDM in twin and singleton gestations.

Results Of 270,843 women who met inclusion criteria, 266,942 (98.6%) and 3901 (1.4%) had a singleton and a twin pregnancy, respectively. Women with twins had a significantly higher risk for overall GDM (aRR = 1.13, 95% CI 1.01–1.28) and diet-treated GDM (aRR = 1.20, 95% CI 1.01–1.42) while the association with insulin-treated GDM was not significant (aRR = 1.07, 95% CI 0.89–1.28). Maternal age ≥ 35 years, non-Caucasian ethnicity and BMI > 30 kg/m^2 were independent risk factors for GDM among women with twins and singletons, and the magnitude of the association of these factors with GDM was similar.

Conclusions Women with twins are at increased risk of GDM, mainly due to a higher rate of diet-treated GDM. Despite higher baseline risk of GDM in women with twins, the effect of known risk factors for GDM is similar to that observed in singletons.

Keywords Diet · Gestational diabetes mellitus · Incidence · Risk factors · Twins

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Introduction

Many of the common obstetrical complications such as preeclampsia, preterm birth, and fetal growth restriction, have been clearly shown to be more common in twin pregnancies when compared to singletons [1]. However, whether the risk of gestational diabetes mellitus (GDM) is also increased in women with twins has been a matter of debate [2–9]. Given the increased placental mass, and subsequently the higher levels of placental hormones with diabetogenic effects (e.g., human placental lactogen and steroidal hormones), it may be expected that the degree of insulin resistance and consequently the rate of GDM would be higher in twins [10, 11]. However, at the same time, the presence of two fetuses and the higher maternal basal metabolic rate may be associated with increased utilization of glucose, which may counteract to some degree the increased insulin resistance [12, 13].

Indeed, while several studies have reported an increased risk for GDM in women with twins [2–5], others did not find a difference in the risk of GDM between twin and singleton pregnancies [6–9]. One possible explanation for these conflicting results may be the lack of adequate adjustment for potential confounding variables since multiple gestations are associated with several factors that are known to increase the risk of GDM, including advanced maternal age [14] and maternal obesity [3, 15]. In addition, many of the previously published studies did not differentiate between the type of GDM (diet vs. insulin treated) [2, 3, 16], information which is important to understand the potential clinical implications of the higher rate of GDM in twin pregnancies.

In addition, given the physiological differences between twin and singleton pregnancies and the possible difference in the baseline risk of GDM between these groups, the impact of known risk factors for GDM may vary between these groups. Information on risk factors for GDM in twin pregnancies is of interest as it may assist care providers in identifying women with twins who are at an increased risk of GDM [5, 10, 17]. However, data on risk factors for GDM in twin compared with singleton pregnancies are limited [2, 8].

Thus, the aim of the current study was to compare the incidence of GDM and risk factors for GDM between twin and singleton pregnancies using a large provincial population-based cohort with detailed information regarding relevant confounding variables.

Materials and methods

Study population

This was a retrospective population-based study of all women who had a singleton or twin hospital birth in Ontario, Canada, between April 2012 and March 2016. Data were obtained from the Better Outcomes Registry and Network (BORN) Ontario (https://www.bornontario.ca/en/about-born/). BORN Ontario is a province-wide registry of all births in Ontario, Canada. Whenever a woman is admitted to hospital to give birth, data are collected by health care providers and hospital staff from charts, clinical forms and patient interview, and then entered into the BORN Information System (either directly or by electronic upload from a hospital's EMR system). The BORN Information System contains maternal demographics, health behaviors and reproductive history, as well as clinical information related to pregnancy, labor, birth and fetal and neonatal outcomes. An ongoing program of data verifications, quality checks, and formal training sessions for individuals collecting and entering data assures a high level of data quality is maintained.

Women were classified into two groups based on plurality: singletons and twins. Women with any of the following conditions were excluded from both groups: gestational age at birth $< 28^{0/7}$ weeks (i.e., prior to routine screening for GDM) or $> 42^{0/7}$ weeks, high-order multiple gestations; maternal age < 19 years, pre-existing diabetes, pregnancies complicated by genetic or structural fetal anomalies, or cases with missing data. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Diagnosis of GDM

This study spans two time periods with regards to criteria for diagnosis of GDM in Ontario. Up until April 2013, the criteria for diagnosis were according to 2008 Canadian Diabetes Associations (CDA) guidelines [11]. These guidelines recommended screening for GDM using a 50-g glucose challenge test (GCT), and when positive (> 7.8 mmol/L or 140 mg/dL), a 75-g oral glucose tolerance test (OGTT) followed (cutoff values: fasting ≥ 5.3 mmol/L or 96 mg/dL; 1 h ≥ 10.6 mmol or 191 mg/dL; 2 h ≥ 8.9 mmol/L or 160 mg/dL). GDM was defined as ≥ 2 abnormal OGTT values or a GCT result of ≥ 10.3 mmol/L or 185 mg/dL. The presence of a single abnormal OGTT value was defined as impaired glucose tolerance (IGT).

In April 2013, new CDA criteria were published [18]. The new guidelines allowed two options for screening/

testing for GDM. The "Preferred" option was essentially identical to the CDA 2008 guidelines aside from increasing the diagnostic 50-g GCT value from 10.3 mmol (185 mg/dL) to ≥ 11.1 mmol (200 mg/dL), and the 2-h 75-g OGTT threshold from 8.9 mmol/L (160 mg/dL) to 9.0 mmol/L (162 mg/dL). The distinction between IGT and GDM was eliminated in these new guidelines.

Data analysis

Baseline characteristics and rate of GDM were compared between the twins and singletons groups. The chi-square and Fisher's exact tests were used for categorical variables and the Mann–Whitney *U* test was used for continuous variables. Modified Poisson regression model with robust error variance was used to calculate the risk ratios for GDM in twin pregnancies (using singleton pregnancies as reference) while adjusting for variables that were found to be different between twins and singletons in the bivariate analysis or variables that are known to be associated with GDM such as pre-pregnancy BMI and ethnicity.

To identify risk factors for GDM among twin and singleton pregnancies, the characteristics of women with twins and GDM were compared with those with twins without GDM. Similar separate comparison was performed for women with singleton pregnancies with and without GDM. A modified Poisson regression model was used to identify independent risk factors for GDM among twins and among singletons, while adjusting for variables that were found to be different between women with and without GDM in the bivariate analysis.

Data were analyzed using the SAS statistical software version 9.4. Significance was set at a two-sided p value < 0.05.

Results

Characteristics of the study population

A total of 561,798 women gave birth in Ontario, Canada, during the study period. Of the 270,843 women who met the inclusion criteria, 266,942 (98.6%) and 3901 (1.4%) had a singleton and a twin pregnancy, respectively (Fig. 1).

The characteristics of women with singleton and twin gestations are presented in Table 1. Women with twins were older, were more likely to be nulliparous and to have a history of pre-existing hypertension, were less likely to smoke and had a higher BMI, although the absolute differences between the groups in all these variables were small. Although women in both groups were mostly of Caucasian ethnicity, women in the twins group were more likely to be Caucasians and less likely to be of Asian ethnicity (Table 1). Finally, women with twins were more likely to conceive following fertility treatments compared to singletons (Table 1).

Risk of GDM in twins and singletons

The incidence of GDM in the twins and singletons groups is presented in Table 2. Women with twins had a higher rate of overall GDM (8.4 vs. 6.3%, $p < 0.001$), diet-treated GDM (4.8 vs. 3.5%, $p < 0.001$), and insulin-treated GDM (3.6 vs. 2.7%, $p = 0.001$) compared with singletons

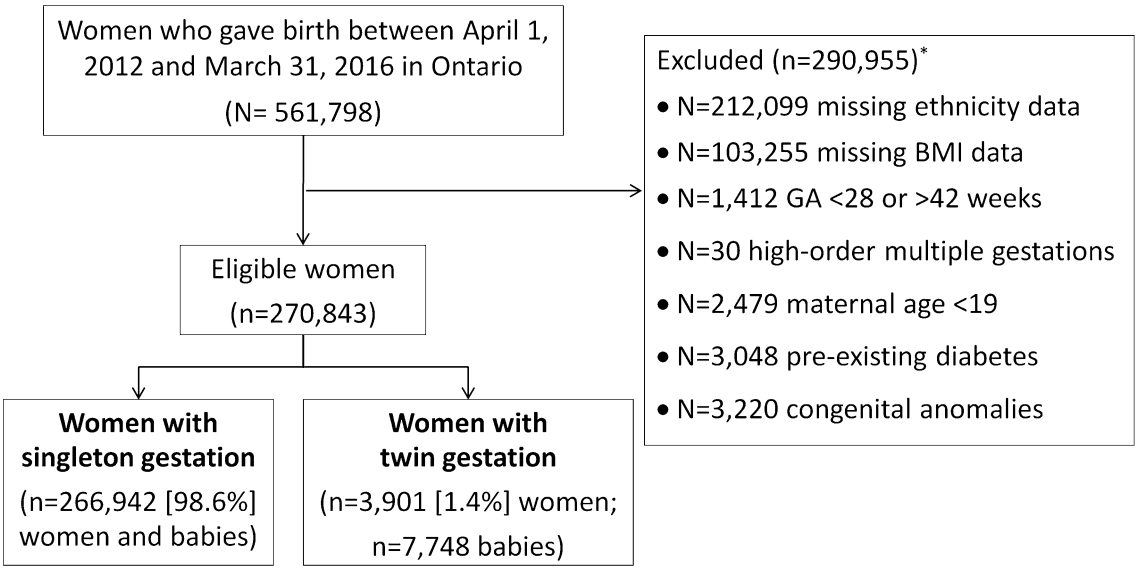

Fig. 1 Selection of the study group. *Exclusion criteria are not mutually exclusive

Table 1 Characteristics of women in the singletons and twins groups

Characteristic	Singleton groups ($N=266,942$)	Twin groups ($N=3901$)	p value
Maternal age (years)	31.0 (28.0–35.0)	33.0 (29.0–36.0)	**< 0.001**
Maternal age ≥ 35 years	67,569 (25.3)	1322 (33.9)	**< 0.001**
Ethnicity			
Caucasian	170,342 (63.8)	2661 (68.2)	**< 0.001**
Asian	65,886 (24.7)	751 (19.3)	**< 0.001**
Black	16,458 (6.2)	265 (6.8)	0.106
Other	14,256 (5.3)	224 (5.7)	0.268
Nulliparity	120,524 (45.1)	1833 (47.0)	**0.042**
Pre-pregnancy BMI (kg/m^2)	23.7 (21.1–27.6)	24.2 (21.5–28.4)	**< 0.001**
<18.5 kg/m^2	14,081 (5.3)	157 (4.0)	**0.001**
18.5–24.9 kg/m^2	146,117 (54.7)	2029 (52.0)	**0.001**
25–29.9 kg/m^2	62,210 (23.3)	956 (24.5)	0.078
30–34.9 kg/m^2	26,064 (9.8)	424 (10.9)	**0.021**
≥ 35 kg/m^2	18,470 (6.9)	335 (8.6)	**< 0.001**
Pre-existing hypertension	2145 (0.8)	43 (1.1)	**0.039**
Smoking	21,272 (8.0)	268 (6.9)	**0.012**
Fertility treatment	9208 (3.4)	1097 (28.1)	**< 0.001**
In vitro fertilization	4450 (1.7)	725 (18.6)	**< 0.001**
Ovulation induction	4647 (1.7)	367 (9.4)	**< 0.001**

Data are presented as median (IQR) or N (%)

Significant p values are emphasized in bold font

BMI body mass index

Table 2 Association between twin gestation and gestational diabetes

Type of GDM	Rate of GDM			Association of twin gestation (using singleton gestation as reference) with GDM	
	Singleton groups ($N=267,503$)	Twin groups ($N=3964$)	p value	Crude RR (95% CI)	Adjusted RR (95% CI)*
Overall	16,731 (6.3)	326 (8.4)	**< 0.001**	**1.33 (1.2–1.48)**	**1.13 (1.01–1.28)**
Diet treated	9431 (3.5)	186 (4.8)	**< 0.001**	**1.35 (1.17–1.55)**	**1.20 (1.01–1.42)**
Insulin treated	7300 (2.7)	140 (3.6)	**0.001**	**1.31 (1.11–1.55)**	1.07 (0.89–1.28)

Significant p values and associations are emphasized in bold font

GDM gestational diabetes, *RR* risk ratio, *CI* confidence interval

*Values represent the results of modified Poisson regression model and are adjusted for maternal age, parity, ethnicity, maternal pre-pregnancy obesity, and assisted reproductive technology

(Table 2). When adjusted for potential confounding variables (including maternal age, parity, ethnicity, maternal pre-pregnancy obesity, and assisted reproductive technology), women with twins had a significantly higher risk for overall GDM (aRR = 1.13, 95% CI 1.01–1.28) and diet-treated GDM (aRR = 1.20, 95% CI 1.01–1.42) while the association with insulin-treated GDM became non-significant (aRR = 1.07, 95% CI 0.89–1.28) (Table 2).

Risk factors for GDM in twin and singleton gestations

To identify risk factors for GDM in twin and singleton gestations, we compared the characteristic of women with and without GDM in the twins group, and a similar separate comparison was performed for women in the singletons group (Table 3).

Table 3 Comparison of characteristics of women with and without gestational diabetes in the singleton and twin groups

Characteristic	Singleton groups			Twin groups		
	GDM ($N=16,731$)	No GDM ($N=250,211$)	p value	GDM ($N=326$)	No GDM ($N=3575$)	p value
Maternal age (years)	33.0 (30.0–36.0)	31.0 (28.0–34.0)	<0.001	34.0 (31.0–37.0)	32.0 (29.0–36.0)	**<0.0001***
Maternal age ≥35 years	6428 (38.4)	61,141 (24.4)	**<0.001**	155 (47.5)	1167 (32.6)	**<0.001**
Ethnicity						
Caucasian	7257 (43.4)	163,085 (65.2)	**<0.001**	170 (52.1)	2491 (69.7)	**<0.001**
Asian	7482 (44.7)	58,404 (23.3)	**<0.001**	115 (35.3)	636 (17.8)	**<0.001**
Black	937 (5.6)	15,521 (6.2)	**0.002**	16 (4.9)	249 (7.0)	0.158
Other	1055 (6.3)	13,201 (5.3)	**<0.001**	25 (7.7)	199 (5.6)	0.118
Nulliparity	6776 (40.5)	113,748 (45.5)	**<0.001**	152 (46.6)	1681 (47.0)	0.969
Pre-pregnancy BMI (kg/m^2)	26.4 (22.7–31.4)	23.6 (21.0–27.4)	**<0.001**	26.2 (22.7–30.4)	24.1 (21.4–28.3)	**<0.001**
Pre-pregnancy BMI (kg/m^2)			**<0.001**			**<0.001**
<18.5 kg/m^2	468 (2.8)	13,613 (5.4)	**<0.001**	8 (2.5)	149 (4.2)	0.132
18.5–24.9 kg/m^2	6492 (38.8)	139,625 (55.8)	**<0.001**	134 (41.1)	1895 (53.0)	**<0.001**
25–29.9 kg/m^2	4605 (27.5)	57,605 (23.0)	**<0.001**	94 (28.8)	862 (24.1)	0.058
30–34.9 kg/m^2	2703 (16.2)	23,361 (9.3)	**<0.001**	51 (15.6)	373 (10.4)	**0.004**
≥35 kg/m^2	2463 (14.7)	16,007 (6.4)	**<0.001**	39 (12.0)	296 (8.3)	**0.023**
Pre-existing hypertension	314 (1.9)	1831 (0.7)	**<0.001**	7 (2.1)	36 (1.0)	0.059
Smoking	1106 (6.6)	20,166 (8.1)	**<0.001**	20 (6.1)	248 (6.9)	0.584
Fertility						
In vitro fertilization	440 (2.6)	4010 (1.6)	**<0.001**	79 (24.2)	646 (18.1)	**0.006**
Ovulation induction	491 (2.9)	4156 (1.7)	**<0.001**	30 (9.2)	337 (9.4)	0.894

Data are presented as median (IQR) or N (%)

Significant p values are emphasized in bold font

BMI body mass index

In both the twins and singletons groups, women with GDM were older, were less likely to be of Caucasian ethnicity, had a higher BMI, and were more likely to conceive by in vitro fertilization compared with women without GDM (Table 3). Among women with singletons, those with GDM were also more likely to be nulliparous, were more likely to have pre-existing hypertension and were less likely to smoke compared with those without GDM (Table 3).

In an adjusted analysis, maternal age ≥35 years, non-Caucasian ethnicity and BMI >30 kg/m^2 were independent risk factors for GDM in both the twin and singleton groups, and the magnitude of association between these factors and GDM was similar for both groups (Table 4). This is also demonstrated when assessing the relationship of maternal age and BMI with GDM in a continuous manner (Fig. 2). Despite the higher baseline rate of GDM in women with twins, the rate of GDM increased in a similar continuous manner in both twins and singletons with maternal age (Fig. 2a) and maternal BMI (Fig. 2b). Fertility treatments were identified as an independent risk factor for GDM among women with singleton but not for women with twins (Table 4).

Comment

Principal findings of the study

In the current study, we aimed to evaluate the association of plurality with the risk of GDM and to compare risk factors of GDM between twin and singleton gestations. Our main findings are: (1) women with twins are at a significantly higher risk for GDM compared with singletons, mainly due to an increased risk for mild (diet-treated) GDM; (2) risk factors for GDM in twin gestations are similar to those identified in singletons, and the magnitude of association of these factors with GDM is similar in both groups.

Results of the study in the context of other observations

Previous studies have shown that the rate of GDM in twin gestations ranges between 3 and 9% [2, 5, 9, 10, 14–16, 19–24], which is in accordance with our results (8.4%). However, with regard to the question of whether women with twins are at increased risk of GDM compared with women with a singleton pregnancy (similar to what is known

Table 4 Factors associated with gestational diabetes in the twin and singleton groups—multivariable analysis

Factor	Singleton gestations Adjusted RR (95% CI)*	Twin gestations Adjusted RR (95% CI)*
Maternal age ≥ 35 years (vs. < 35 years)	**1.73 (1.67–1.79)[a]**	**1.76 (1.39–2.24)[f]**
Non-Caucasian ethnicity (vs. Caucasian)	**2.55 (2.47–2.63)[b]**	**2.11 (1.67–2.68)[g]**
Nulliparity (vs. multiparity)	1.02 (0.99–1.05)[c]	0.94 (0.74–1.2)[h]
BMI > 30 kg/m^2 (vs. ≤ 30 kg/m^2)	**2.39 (2.31–2.47)[d]**	**1.98 (1.54–2.55)[i]**
Fertility treatment (vs. no treatment)	**1.50 (1.4–1.6)[e]**	1.22 (0.95–1.57)[j]

Significant *p* values are emphasized in bold

BMI body mass index, *RR* risk ratio, *CI* confidence interval

*Values reflect the results of a Poisson regression model adjusted for the variables listed below

[a]Adjusted for parity, ethnicity groups, obesity, and assisted reproductive technology

[b]Adjusted for maternal age, parity, obesity, and assisted reproductive technology

[c]Adjusted for maternal age, ethnicity groups, obesity, and assisted reproductive technology

[d]Adjusted for maternal age, parity, ethnicity groups, and assisted reproductive technology

[e]Adjusted for maternal age, parity, ethnicity groups, and obesity

[f]Adjusted for parity, ethnicity groups, obesity, assisted reproductive technology, pre-existing hypertension, and smoking

[g]Adjusted for maternal age, parity, obesity, assisted reproductive technology, pre-existing hypertension, and smoking

[h]Adjusted for maternal age, ethnicity groups, obesity, assisted reproductive technology, pre-existing hypertension, and smoking

[i]Adjusted for maternal age, parity, ethnicity groups, assisted reproductive technology, pre-existing hypertension, and smoking

[j]Adjusted for maternal age, parity, ethnicity groups, obesity, pre-existing hypertension, and smoking

for other pregnancy complications such as preterm birth and preeclampsia), data are conflicting. While some found, in agreement with our findings, that women with twins are at increased risk of GDM compared with singletons [2, 3, 5, 14, 24], other failed to detect such a difference in the risk of GDM between twins and singletons [8, 9, 15, 23]. This controversy may be attributed, at least in part, to limitations of previous studies including small sample size which may result in a type-2 error [2, 3, 8, 9, 14, 24], and lack of adjustment for potential confounding variables such as pre-pregnancy BMI and maternal ethnic group [5, 9, 15, 24]. In addition, many of the studies did not provide data on the type of GDM, information that is important to understand the potential clinical implications of the higher rate of GDM in twin pregnancies. The importance of the current study lies in our large cohort of both singleton and twin pregnancies and the adjustment for major confounders, such as BMI and maternal ethnicity, which helped to determine the true effect of plurality on the rate of GDM in general and on the rate of the subtypes of GDM (i.e., diet and insulin treated).

We found that even after adjustment for known risk factors for GDM, women with twins are at an increased risk for GDM compared to women with singletons. Although the reasons for the increased risk of GDM in twins are unclear, the greater placental mass in twins [25, 26] is likely to play an important role. Previous studies have shown a positive relationship between placental mass and the risk of GDM [27, 28], most probably due to the higher levels of the diabetogenic hormone human placental lactogen (hPL) [29, 30]. However, based on our finding that the increased risk for GDM in twins is limited to diet-treated GDM, it seems that the degree of glucose intolerance in twins is only mildly impaired compared with singletons. It may be argued that this mild increase in glucose intolerance in twin pregnancies may be viewed as normal physiologic change inherent to twin pregnancies which may have a beneficial role (i.e., matching glucose availability to the increased demand for glucose in twin pregnancies) rather than a pathology that needs to be diagnosed and treated, similar to many of the other physiologic changes of pregnancy that are amplified in twin gestations [31]. According to this argument, the apparent 'increased risk' of GDM in twin pregnancies is merely the result of the fact that we use the same thresholds for screening and diagnosis of GDM in twins and singletons despite the obvious physiological differences. Indeed, it has been shown that 50-g GCT has a higher false positive rate for GDM in twin compared with singleton gestations [6] and was suggested that different threshold should be used for screening for GDM in twin gestations [32]. Additional support to this argument comes from the observation that women who experienced GDM in the presence of a twin pregnancy were significantly less likely to develop future type-2 diabetes compared with those who had GDM in a singleton pregnancy (HR 0.76, 95% CI 0.65–0.90) [5]. In

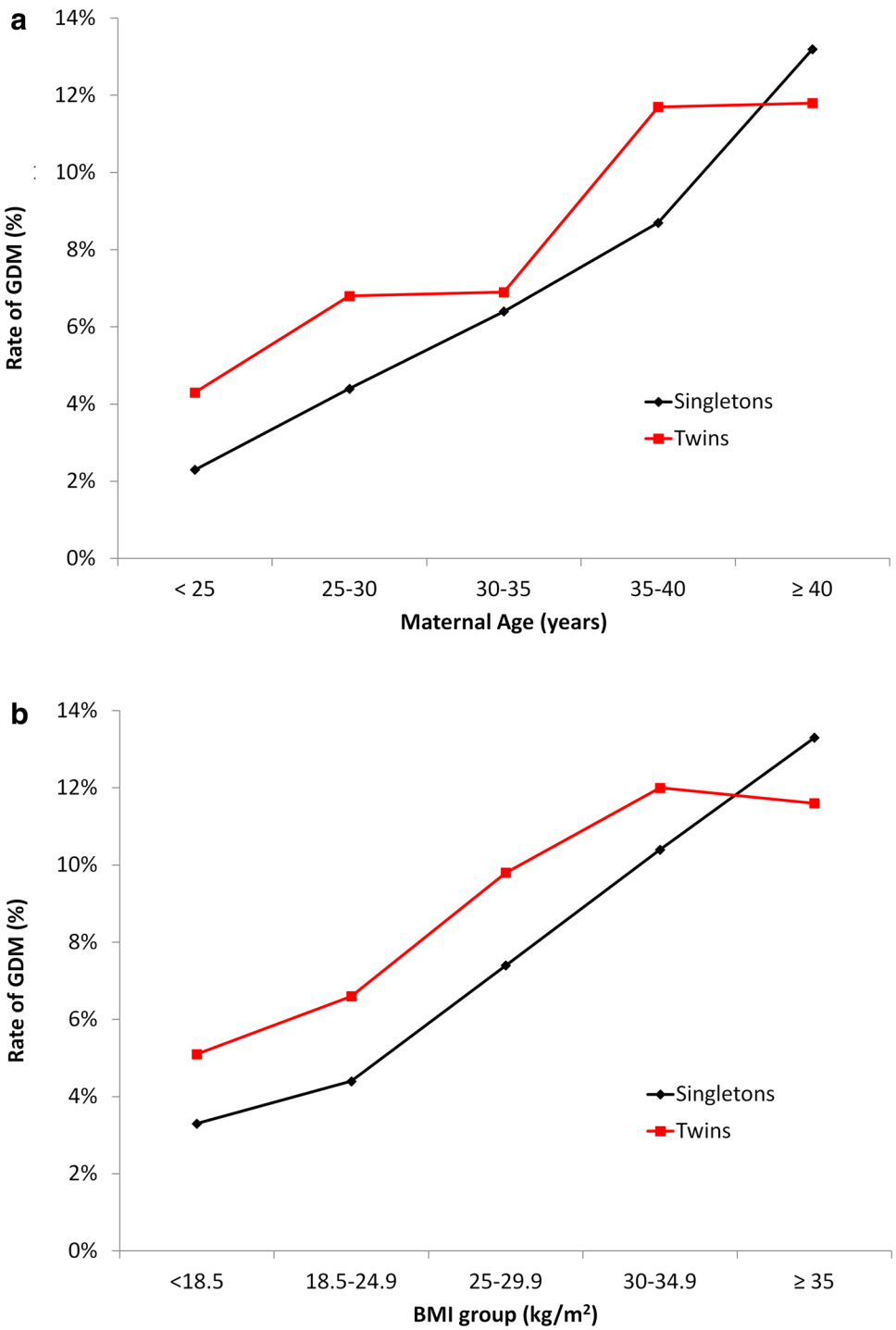

Fig. 2 Rate of gestational diabetes mellitus by maternal age and BMI in the twins and singletons groups. Rate of GDM in women with singleton (black line) and twin (red line) pregnancies by maternal age group (**a**) and BMI group (**b**). *GDM* gestational diabetes mellitus, *BMI* body mass index

contrast, we have recently demonstrated that GDM and milder degrees of glucose intolerance are associated with an increased risk of asymmetric overgrowth in twin pregnancies, which may provide support to current screening and diagnosis criteria for GDM [19].

We found that the type and magnitude of risk factors for GDM are similar between twins and singletons. Only a few studies reported on risk factors for GDM in twins pregnancies. In concordance with our results, Lucovnik et al. [33] reported that high BMI was an independent risk factor for GDM in both twin and singleton gestations. Similarly, in agreement with our findings, Wang et al. [4] reported that assisted reproductive technology increases the likelihood of GDM in singletons (aOR = 1.26, 95% CI = 1.18–1.36), but not in twins. The reason for the discordance in association with fertility treatments with GDM between twins and

singleton is unclear but we speculate that it may be related to differences in the distribution of the indications for fertility treatments in both groups, for example, differences in the proportion of women with ovulation dysfunction due to polycystic ovary syndrome (PCOS), and independent risk factor for GDM [34].

Strengths and limitations

The main strength of our study is the population-based nature of the study and the large sample size of both twin and singleton pregnancies, which made our study powered to detect differences between twins and singletons not only in the overall rate of GDM but also in the rate of subtypes of GDM (i.e., diet-treated vs. insulin-treated GDM). Another strength is the availability of data on important confounding variables which were not accounted for in some of the previous studies on this topic [3, 15]. Still, our study has several limitations. Due to its retrospective nature, information on several potentially confounding variables such as GDM in previous pregnancies, history of PCOS and family history of diabetes [35, 36] was unavailable for analysis. Another limitation is the potential selection bias given the fact that about 50% of the initial population was excluded due to missing data on pre-pregnancy BMI or ethnicity. Still, we believe that including those cases with missing information on BMI or ethnicity would result in an even greater bias due to the failure to adjust the analysis for these important confounding variables.

Conclusion

Our findings suggest that women with twins are at increased risk of GDM, mainly due to a higher rate of mild (diet-treated) GDM. The similarity in risk factors for GDM in twin and singleton pregnancies implies that GDM represents the same disease in both groups and that despite the higher baseline risk of GDM in twins, the effect of known risk factors for GDM in twin pregnancies is similar to that observed in singletons. Care providers should consider twin pregnancy as an independent risk factor for GDM when assessing patients risk for GDM, and studies on GDM should adjust for twin gestation as an independent risk factor for GDM.

Author contributions LH researched data, wrote the manuscript and reviewed/edited the manuscript. HB reviewed the protocol involved in study design, reviewed and edited the manuscript. RO involved in the study design, protocol development, literature search. JGR reviewed and edited the manuscript. MG reviewed and edited the manuscript. SDM reviewed and edited the manuscript. BMD reviewed and edited the manuscript. RC data extraction, data analysis. IH involved in the conception of the study, writing of the protocol. HH data extraction, data analysis. JB assisted with the conception of the study, design, manuscript writing. NM researched data, wrote the manuscript and reviewed/edited the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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