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ORIGINAL ARTICLE ***Reproductive epidemiology***

Maternal hyperglycemia in singleton pregnancies conceived by IVF may be modified by first-trimester BMI

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STUDY QUESTION: Does IVF independently increase the risk of gestational diabetes mellitus (GDM) and is this increase in risk modified by maternal body mass index?

SUMMARY ANSWER: IVF appears to be an independent risk factor for GDM and elevated blood glucose levels in overweight women (BMI > 25 kg/m^2).

WHAT IS KNOWN ALREADY: IVF has been associated with increased risk of GDM, but most previous studies did not adequately assess confounding or effect modification by other risk factors.

STUDY DESIGN, SIZE, DURATION: Cross-sectional study using data from 1089 women with singleton pregnancies who participated in a Singaporean birth cohort study (GUSTO) and received a 75 g oral glucose tolerance test (OGTT) at 26–28 weeks gestation.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 1089 women (n = 1013 conceived spontaneously, n = 76 conceived through IVF) with singleton pregnancies received a 75 g OGTT at 26–28 weeks gestation. Fasting and 2 h postprandial blood glucose levels were assayed. World Health Organization criteria (1999) standard criteria were used to classify GDM: ≥7.0 mmol/L for fasting and/or ≥7.8 mmol/L for 2-h postprandial plasma glucose levels, which was the clinical guideline in use during the study.

MAIN RESULTS AND THE ROLE OF CHANCE: IVF pregnancies had nearly double the odds of GDM (OR = 1.83, 95% CI: 1.03–3.26) and elevated fasting (mean difference = 0.12 mmol/L, 95% CI: 0.00–0.24) and OGTT 2-h blood glucose levels (mean difference = 0.64 mmol/L, 95% CI: 0.27–1.01), after adjusting for commonly recognized risk factors for GDM. After stratification by first-trimester BMI, these increased risks of GDM (OR = 3.54, 95% CI: 1.44–8.72) and elevated fasting (mean difference = 0.39 mmol/L, 95% CI: 0.13–0.65) and 2-h blood (mean difference = 1.24 mmol/L, 95% CI: 0.56–1.91) glucose levels were significant only in the IVF group who is also overweight or obese (BMI > 25 kg/m^2).

LIMITATIONS REASONS FOR CAUTION: One limitation of our study is the absence of a 1 h post-OGTT plasma glucose sample, as we were using the 1999 WHO diagnostic criteria (the clinical guideline in Singapore) at the time of our study, instead of the revised 2013

WHO diagnostic criteria. Our cohort may not be representative of the general Singapore obstetric population, although participants were recruited from the two largest maternity hospitals in the country and include both private and subsidized patients.

WIDER IMPLICATIONS OF THE FINDINGS: IVF appears to be an independent risk factor for GDM and elevated blood glucose levels in overweight women. Our findings reinforce the need to advise overweight or obese women contemplating IVF to lose weight before the procedure to reduce their risk of GDM and hyperglycemia-related adverse outcomes arising therefrom. In settings where universal GDM screening is not routine, overweight or obese women who conceive by IVF should be screened.

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Key words: IVF / gestational diabetes / overweight / blood glucose / BMI

Introduction

Since the first birth conceived by IVF in 1978, the number of women receiving ART is increasing worldwide, with over 5 million children born with the help of ART (Kissin *et al.*, 2014). With its increasing use and success, it is important to consider ART's effects on maternal and child outcomes. Systematic reviews and meta-analyses have shown that women who conceived through IVF are at higher risk of pregnancy complications including hypertensive disorders and gestational diabetes (Jackson *et al.*, 2004; Pandey *et al.*, 2012). These increased risks may be partly attributable to multiple pregnancies (Qin *et al.*, 2015), but studies have increasingly reported higher risks in singleton pregnancies as well (Helmerhorst *et al.*, 2004; Pandey *et al.*, 2012).

Many prior studies of ART and pregnancy complications examined a large number of pregnancy and perinatal complications, including gestational diabetes, pre-eclampsia, premature rupture of membranes and preterm birth (Jackson *et al.*, 2004; Pandey *et al.*, 2012; Qin *et al.*, 2015; Zhu *et al.*, 2016). Traditional risk factors for gestational diabetes mellitus (GDM), including family history of diabetes and previous GDM history, are rarely considered when comparing IVF and spontaneously conceived pregnancies. GDM is known to increase the risks of subsequent type 2 diabetes in the mother (Bellamy *et al.*, 2009), adverse birth outcomes such as preterm birth, macrosomia, and neonatal hypoglycemia (Hay, 2012), and long-term offspring obesity, diabetes and cardiovascular diseases (Fraser and Lawlor, 2014). Given the increasing incidence of GDM (Buckley *et al.*, 2012), it is important to establish whether IVF is an independent risk factor for GDM development. Additionally, amongst all the classic risk factors for GDM (Guideline Development Group, 2008), only maternal BMI is modifiable. We further hypothesized that overweight and obese women who underwent IVF would be more susceptible to GDM than underweight or normal-weight women, i.e. that first-trimester maternal BMI would modify the association of IVF with GDM and maternal blood glucose levels.

Materials and Methods

Study design and population

Data were obtained from Growing Up in Singapore Towards healthy Outcomes (GUSTO), a mother-offspring prospective cohort study in Singapore. From June 2009 to September 2010, 1247 (1162 who conceived spontaneously and 85 who conceived via IVF) pregnant women aged 18 years and above were recruited at 11–14 weeks of gestation from two major public maternity units in Singapore: KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). Details on the study have been previously published (Soh *et al.*, 2014). We excluded women who had Type 1 diabetes mellitus or were receiving chemotherapy or psychotropic drugs.

Maternal characteristics

Maternal demographic and clinical data were collected at multiple study visits. Data on age, ethnicity, educational level, pre-pregnancy BMI, family history of diabetes, menstrual history and obstetric history of GDM and delivery data from previous pregnancies were obtained by interviewer administered questionnaire at the recruitment visit. Data on parity, first-trimester BMI were obtained from hospital medical records.

Oral glucose tolerance test and GDM diagnosis

All participants who attended the clinic visit at 26–28 weeks of gestation were offered a 75 g oral glucose tolerance test (OGTT) after 8–10 h of overnight fasting; fasting and 2-h venous blood samples were collected in fluoride tubes. Fasting and 2-h postprandial plasma glucose concentrations were measured by colorimetry [Advia 2400 Chemistry system (Siemens Medical Solutions Diagnostics) and Beckman LX20 Pro analyzer (Beckman Coulter)] (Chong *et al.*, 2014). World Health Organization criteria (1999) standard criteria were used to classify GDM: ≥7.0 mmol/L for fasting and/or ≥7.8 mmol/L for 2-h postprandial plasma glucose levels (2013), which was the clinical guideline in use during the study.

As we did not measure baseline blood glucose levels during first trimester, we included a sensitivity analysis, excluding participants with

probable undiagnosed Type 2 diabetes defined as a fasting glucose ≥7.0 mmol/L or 2 h glucose ≥11.1 mmol/L at the 26–28 weeks OGTT (2013).

Statistical analysis

Continuous and categorical maternal characteristics were compared between spontaneous conception and IVF mothers using independent sample *t*-tests and chi-square tests, respectively. Multivariable logistic regression models were used to estimate the odds ratio (OR) of GDM in IVF versus spontaneous conceptions. Multivariable linear regression models were used to assess the mean difference in fasting and 2 h post-OGTT glucose levels between the two conception groups. All multivariable models adjusted for maternal age, ethnicity, first-trimester maternal BMI, family history of diabetes, previous history of GDM and prior history of a macrosomic (>4 kg) infant. To test the hypothesis that overweight and obese women may be more susceptible to GDM than their underweight or normal weight counterparts, we included a multiplicative interaction term in the multivariable logistic and linear regression models, respectively. As these interaction terms were statistically significant or near significant (all $P < 0.10$), we further stratified our analyses by BMI: under/normal weight (<25 kg/m^2) compared with overweight/obese (≥25 kg/m^2). No other effect modifiers were hypothesized, and no other interactions were assessed. Additional sensitivity analysis was done, where missing first-trimester BMI was replaced with self-reported pre-pregnancy BMI. All analyses were carried out using SPSS version 24.0 (IBM, Armonk, NY, USA).

Ethical approval

This study followed the principles of the Declaration of Helsinki. The study received approval from ethics committees of the hospitals involved: SingHealth Centralized Institutional Review Board and National Healthcare Group Domain Specific Review Board in Singapore. Written informed consent was obtained from all participants.

Results

Participant characteristics

Figure 1 shows the study flow diagram. We excluded participants who were lost to follow-up ($n = 32$) and did not complete the OGTT at 26–28 weeks because of a missed visit ($n = 33$) and refusal or unable to complete OGTT ($n = 81$), had multiple pregnancies ($n = 10$) or previously diagnosed type 2 diabetes ($n = 1$) or were not of homogenous ethnicity ($n = 1$). Participants who were excluded ($n = 158$) were comparable to those included in terms of maternal age, first-trimester BMI, previous history of GDM, delivery of a macrosomic baby, family history of diabetes and regularity of their menstrual cycle. However, included women were more likely to be of Chinese ethnicity than those excluded (57.2 versus 45.6%). In total, 1089 participants were included in our analysis, of whom 76 conceived through IVF. Women who conceived by IVF were older, more likely to be of Chinese ethnicity and nulliparous, but less likely to have a family history of diabetes (Table 1).

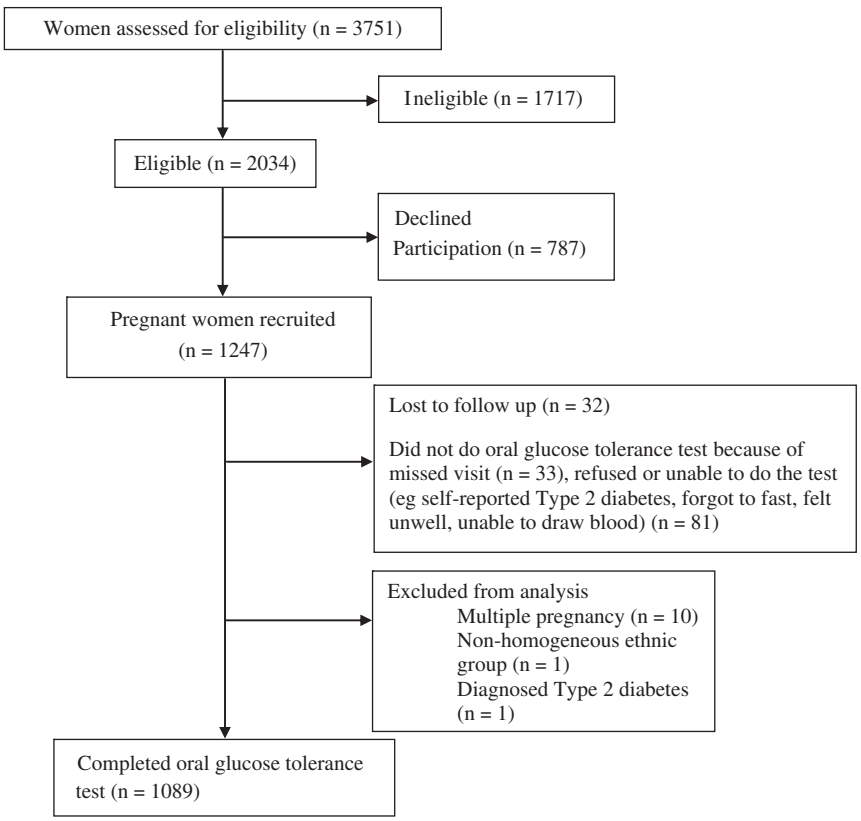

Figure 1 Flowchart describing the recruitment and inclusion of participants from the GUSTO (Growing Up in Singapore toward Healthy Outcomes) birth cohort study.

Mode of conception and its association with GDM risk and glucose levels

In the unadjusted analysis, women who conceived through IVF had more than double the odds of GDM compared to the spontaneous conception group (Table II). After adjusting for maternal age, ethnicity, first-trimester maternal BMI, family history of diabetes, previous history of GDM and prior history of macrosomia, the odds of GDM remained significantly higher in the IVF group (Table II). Similarly, the

Table I Demographic characteristics of mothers with spontaneous conception versus IVF. Data are *n* (%) unless stated otherwise.

Variables	Spontaneous conception (*n* = 1013)	IVF (*n* = 76)	*P*-value
Maternal age (years), mean (SD)	30.4 (5.2)	33.9 (3.1)	<0.001
Ethnicity, *n* (%)			<0.001
Chinese	561 (55.4)	62 (81.6)	
Malay	271 (26.8)	6 (7.9)	
Indian	181 (17.9)	8 (10.5)	
First-trimester BMI			0.251
<25 kg/m^2	661 (65.3)	44 (57.9)	
≥25 kg/m^2	291 (28.7)	26 (34.2)	
Missing, *n* (%)	61 (6.0)	6 (7.9)	
Nulliparous at recruitment	436 (43.0)	62 (81.6)	<0.001
Missing	10 (1.0)	0 (0.0)	
Previous history of Gestational diabetes mellitus	35 (3.5)	0 (0.0)	0.112
Missing	25 (2.5)	7 (9.2)	
Previous delivery of babies >4 kg	17 (1.7)	0 (0)	0.252
Missing	24 (2.4)	1 (1.3)	
Family history of diabetes	310 (30.6)	12 (15.8)	0.006
Missing	25 (2.5)	2 (2.6)	
Menstrual cycle			
Regular	746 (73.6)	51 (67.1)	0.256
Irregular	240 (23.7)	24 (31.6)	
Missing	27 (2.7)	1 (1.3)	
Fasting plasma glucose concentration (mmol/L), mean (SD)	4.35 (0.46)	4.47 (0.65)	0.029
2-h postprandial plasma glucose concentration (mmol/L), mean (SD)	6.49 (1.44)	7.21 (1.78)	<0.001
Gestational diabetes mellitus	179 (17.7)	23 (30.3)	0.006

P-values are determined by chi-square or independent *t*-test.

Table II Association of IVF with maternal glucose concentrations and gestational diabetes mellitus.

	Unadjusted (*n* = 1089)			Adjusted[a] (*n* = 930 versus 63)	
	OR (95% CI)		*P*-value	OR (95% CI)	*P*-value
	Normal (*n* = 1013)	IVF (*n* = 76)			
GDM	Reference	2.02 (1.21–3.39)	0.007	1.83 (1.03–3.26)	0.040
	Mean (SD)			Mean difference (95% CI)	
Fasting glucose (mmol/L)	4.35 (0.46)	4.47 (0.65)	0.029	0.12 (0.00–0.24)	0.050
OGTT 2-h glucose (mmol/L)	6.49 (1.44)	7.21 (1.78)	<0.001	0.64 (0.27–1.01)	0.001

OR, odds ratio; CI, confidence internal; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus.
[a]Adjusted for maternal age, ethnicity, first-trimester maternal BMI, family history of diabetes, previous history of GDM and delivery of macrosomic babies (>4 kg).

Table III Association of IVF with maternal glucose concentrations and gestational diabetes mellitus, stratified by first-trimester body mass index.

	Unadjusted		Adjusted[a]			
	Under/normal weight (BMI < 25 kg/m^2) (n = 661 versus 44)	Overweight/obese (BMI ≥ 25 kg/m^2) (n = 291 versus 26)	Under/normal weight (BMI < 25 kg/m^2) (n = 645 versus 39)		Overweight/obese (BMI ≥ 25 kg/m^2) (n = 285 versus 24)	
	OR[b] (95% CI)		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
GDM	1.44 (0.67–3.09)	3.41 (1.51–7.71)	1.14 (0.51–2.55)	0.744	3.54 (1.44–8.72)	0.006
	Mean difference[b] (95% CI)		Mean difference[b] (95% CI)		Mean difference[b] (95% CI)	
Fasting glucose (mmol/L)	−0.01 (−0.10–0.13)	0.36 (0.11–0.60)	−0.04 (−0.17 to 0.08)	0.524	0.39 (0.13–0.65)	0.003
OGTT 2-hour glucose (mmol/L)	0.54 (0.12–0.97)	1.10 (0.46–1.75)	0.27 (−0.17 to 0.71)	0.227	1.24 (0.56–1.91)	<0.001

OR, odds ratio; CI, confidence internal; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus.
[a]Adjusted for maternal age, ethnicity, family history of diabetes, previous history of GDM and delivery of macrosomic babies (>4 kg).
[b]Reference to control group of women who conceived spontaneously in the respective BMI group.

2 h OGTT blood glucose levels were significantly higher in the IVF group, both before and after adjustment for covariates (Table II). Fasting blood glucose levels were significantly higher in the IVF group before adjustment and continued to show the same trend after covariate adjustment (Table II).

We observed a significant interaction between mode of conception and first-trimester BMI on both fasting and 2 h OGTT blood glucose levels (both *P* for interaction = 0.001), although the interaction was non-significant for risk of GDM (P = 0.080). When stratified by first-trimester BMI, the increase in GDM risk, as well as higher fasting and 2 h OGTT blood glucose, were statistically significant only in women with first-trimester BMI ≥ 25 kg/m^2 (Table III).

Three additional sensitivity analysis was performed. Firstly, where there was missing first-trimester BMI data, this was replaced with self-reported pre-pregnancy BMI. The two BMIs were highly correlated with a correlation coefficient of 0.962. The results are shown in Supplementary Table SI and the findings remained unchanged. Secondly, we excluded probable undiagnosed Type 2 diabetes (n = 8) and the findings remained unchanged (Supplementary Table SII). Lastly, we also carried out a sensitivity analysis adjusting for self-reported menstrual irregularities, as a surrogate for possible polycystic ovarian syndrome or other hormonal disorders that may contribute to GDM; our findings remained unchanged (Supplementary Table SIII).

Discussion

Our findings confirm the association between IVF and GDM risk (Maman *et al.*, 1998; Pandey *et al.*, 2012; Ashrafi *et al.*, 2014; Qin *et al.*, 2017). The association remained after adjusting for key GDM risk factors, namely family history of diabetes, previous history of GDM and previous macrosomic infant, which is a step often omitted in studies of adverse obstetric and perinatal outcomes associated with IVF. To the best of our knowledge, our study is the first to demonstrate effect modification by maternal BMI. Aside from higher rates of GDM, we also showed that IVF is associated with higher fasting and 2 h post-OGTT blood glucose concentrations in late second trimester, especially in overweight and obese women. This is important to note as it has been shown that the risk of adverse birth outcomes increases across the continuum of rising maternal blood glucose levels, even below GDM thresholds (Metzger *et al.*, 2008; Aris, *et al.*, 2014).

Szymanska *et al.* (2011) observed higher first-trimester fasting blood glucose in IVF pregnancies, but not in second-trimester blood glucose levels. Moreover, that study was restricted to women with GDM. Ashrafi *et al.* has carried out similar studies in an Iranian population but did not observe significant differences in blood glucose levels according to mode of conception (IVF, spontaneous and iatrogenic insemination) at both first trimester (fasting) and second trimester (fasting and post-OGTT 1, 2 and 3 h). Their different findings might be attributable to smaller sample sizes (n = 36 and 41) or to differences in the populations studied. The incidences of GDM and type two diabetes are higher in East Asian populations like Singapore.

To our knowledge, ours is the first study to find that first-trimester BMI modifies the effect of IVF on GDM risk and blood glucose levels. Machtinger *et al.* (2015) studied the link between BMI and IVF on adverse obstetric outcomes but found no significant effect of IVF on risk of GDM. However, it is important to note that their study subjects were mainly Caucasians, with much lower risk of GDM (Jenum *et al.*, 2012).

The strengths of our study include the examination of an Asian population, considering Asians are not as well studied as their Caucasian counterparts despite their higher risk of GDM (Jenum *et al.*, 2012). We also adjusted for many key risk factors for GDM, which were often not taken into consideration in previous studies of adverse outcomes following IVF pregnancies. One limitation of our study is the absence of a 1 h post-OGTT plasma glucose sample, as we were using the 1999 WHO diagnostic criteria (the clinical guideline in Singapore) at the time of our study, instead of the revised 2013 WHO diagnostic criteria (2013). We did not measure basal glucose levels of these women during the first trimester, but we added a sensitivity analysis excluding cases with probable undiagnosed Type 2 diabetes and the findings remained unchanged. Moreover, our cohort may not be representative of the general Singapore obstetric population, although participants were recruited

from the two largest maternity hospitals in the country and include both private and subsidized patients.

Our findings suggest that in Asian women who conceive by IVF, the risk of GDM is significantly elevated particularly among those who are overweight or obese. Our results suggest that overweight or obese women should be advised to lose weight before embarking on IVF, to reduce their risk of hyperglycemia and GDM. Most risk-based screening strategies for GDM only included obesity (BMI > 30) as a risk factor (Guideline Development Group, 2008). In the absence of universal screening, overweight or obese women who conceive by IVF, should also be screened for GDM using the OGTT.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

Authors' contributions as follows: P.D.G., K.M.G., F.Y. and Y.S.C. conceived, designed and supervised the cohort study. Y.S.C. and S.C. conceptualized idea for this article. J.K.Y.C., P.C.W., K.H.T., L.P.C.S. and F.Y. were involved in design of questionnaire or protocol as well as supervision of data collection. S.C., P.N., M.S.K., S.Y.C. and Y.S.C. analyzed and interpreted the data. S.C., P.N., M.S.K. and S.Y.C. contributed to the preparation of the article. All authors critically revised the article for intellectual and scientific content and have approved this submission for publication.

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Conflict of interest

K.M.G. and Y.S.C. have received lecture fees from Nestle Nutrition Institute and Danone respectively. K.M.G., Y.S.C. and S.Y.C. are part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone. The other authors have nothing to disclose.

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