Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Combined Impact of High Body Mass Index and *In Vitro* Fertilization on Preeclampsia Risk: A Hospital-Based Cohort Study

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Objectives: Overweight and obese women may be heavy users of *in vitro* fertilization (IVF) owing to obesity-related oligo-anovulation. The higher doses of gonadotropins required to achieve pregnancy in obese women may contribute to impaired placentation and the development of preeclampsia. This study was designed to assess the combined effect of high maternal body mass index (BMI) and IVF on risk of preeclampsia and to evaluate for an interaction between the two factors.

Methods: This is a hospital-based cohort study of 10,013 singleton pregnancies that delivered from 2001 to 2008 at a tertiary hospital in Montreal, Canada. The combined effect of high BMI and IVF on preeclampsia versus no risk factors was estimated in multivariate logistic regression models fitted with an interaction term between high BMI ($>$ 25 or $>$ 30 kg/m^2) and IVF.

Results: IVF pregnancies in obese women had a considerably higher risk of preeclampsia than spontaneous nonobese pregnancies (OR 6.7, 95% CI 3.3-13.8; p interaction 0.03). IVF was not independently associated with preeclampsia (OR 0.6, 95% CI 0.3-1.4). Analyses were similar in subgroup analyses and in analyses correcting for bias.

Conclusions: High BMI is strongly associated with preeclampsia, and this risk is compounded in IVF pregnancies.

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Introduction

The prevalence of obesity is increasing among women (1), and with it, female infertility (2). There is growing demand for assisted reproductive technologies (ART) including *in vitro* fertilization (IVF) that is in part related to delayed childbearing (3) and the increasing proportion of overweight body mass index (BMI = 25 - 30 kg/m^2) and obese (BMI $>$ 30 kg/m^2; 4) reproductive-aged women with ovulatory dysfunction (2). IVF has been associated with a higher risk of preeclampsia in singletons (5), although it is uncertain whether treatment or infertility drives the observed excess risk (6). In areas where IVF is publicly funded under government health insurance programs, there is debate about whether access to IVF should be universal or based on selection criteria that consider costs of treatment and health risks to the woman and her offspring (7). IVF has been publicly funded in Quebec, Canada since 2010 (8), but no formal provincial BMI restrictions for IVF access are in place. Conversely, national guidelines in the UK and elsewhere have advocated using body mass index (BMI) cutoffs for access to infertility treatments (7,9,10).

Restricting access to ART based on BMI may be viewed as discriminatory and is largely based on controversial evidence suggesting reduced ART success rates in obese women (11,12). Furthermore, it has been argued that fertility therapy and research focus attention mainly on achieving pregnancy, overlooking downstream effects in pregnancy and long-term maternal health (13). Specifically, it is unknown whether IVF in overweight and obese women further

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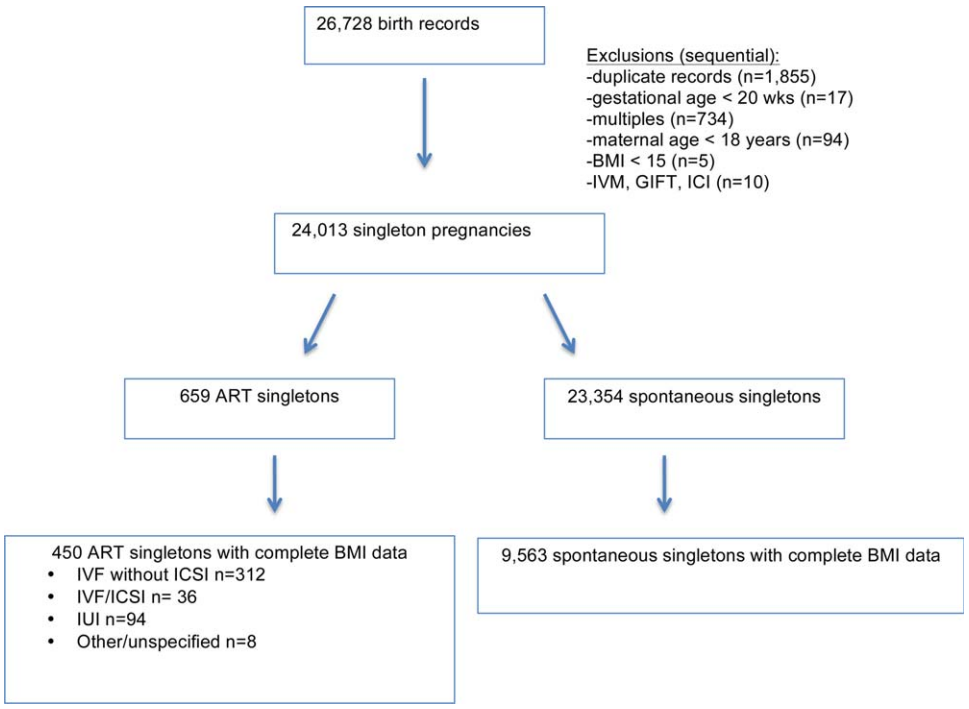

Figure 1 Establishment of study cohort (study flow). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

increases the risk of preeclampsia during the index pregnancy over what might be expected based on high BMI alone. High maternal BMI is strongly associated with preeclampsia (14-17). Preeclampsia has potential serious implications for maternal health both during pregnancy (18,19) and throughout her lifespan (20,21). Thus, an understanding of how ART in general, and IVF specifically, modifies the effect of high BMI on preeclampsia risk would help to inform clinical decisions and policy about access to ART in overweight and obese women. In this study, we aimed to estimate individual and combined effects of high BMI and IVF on the risk of preeclampsia, and assessed for an interaction between high BMI and IVF.

Methods

Participants and data

This was a hospital-based cohort study using clinical data from the McGill Obstetric and Neonatal Database (MOND) from April 1, 2001 to July 1, 2008. MOND records all live births and stillbirths weighing at least 500 grams at a tertiary university hospital in Montreal, Canada. Data entry and coding are completed by a clerk for routine entries, and by three professionals (nurse, obstetrician, and neonatologist) for items requiring critical clinical decisions (22). The database is managed and overseen by the Department of Pediatrics (Neonatalogy) at the McGill University Health Centre. We supplemented prenatal maternal height and weight with data from McGill Reproductive clinic charts matched to the index pregnancy in MOND.

We restricted analyses to pregnancies delivered after 20 weeks gestation (calculated using date of last normal menstrual period, if available, or estimated date of confinement by ultrasound otherwise) since preeclampsia is not diagnosed before this time, and to mothers aged 18 or older, since ART is typically reserved for adults. We excluded assisted pregnancies conceived using intracervical insemination, *in vitro* maturation, and gamete intrafallopian tube transfer since these are not part of the standard definition of ART ($n = 10$; 23). We also excluded multiple births ($n = 734$), because preeclampsia and other perinatal risks are more common in this population (24) and because of the shift toward mandatory single embryo transfers in centers offering government-funded ART (25). We report results from a "complete case" analysis, using records with prenatal height and weight derived either from the first antenatal obstetric visit or at the first visit with a fertility specialist, and statistically imputed remaining missing data in a sensitivity analysis. We evaluated all eligible pregnancies with prepregnancy BMI at least 15 kg/m^2 (Figure 1).

Definition of preeclampsia

We evaluated the occurrence of preeclampsia as a binary outcome, with or without complications, such as eclampsia or the hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. This was a clinical diagnosis documented in the patient's chart by a physician. According to recent Canadian guidelines, preeclampsia is defined as a [sustained] diastolic blood pressure > 90 mmHg in conjunction with urinary protein excretion of at least 300 mg/24 h or with adverse maternal or fetal conditions (thrombocytopenia, elevated liver enzymes, pulmonary edema, stroke, or intrauterine growth restriction) occurring after 20 weeks gestation (18). This classification closely resembles the Canadian Hypertension Society (26), as well as American College of Obstetrics and Gynecology

guidelines defining hypertensive disorders of pregnancy during our study period (27).

Definitions of study exposures

The main study exposure was an elevated prepregnancy BMI [weight, kg/(height, m)^2], with two lower-limit cutoffs chosen at or above 25 and 30 kg/m^2 based on the World Health Organization definitions for overweight and obesity, respectively (4). These cutoffs are clinically meaningful given the well-recognized association between BMI above these levels and preeclampsia risk. Furthermore, dichotomizing BMI in the analyses could provide relevant and applicable information regarding the use of BMI cutoffs for access to IVF. However, given the demonstrated linear association between increasing BMI and preeclampsia (14), we also evaluated BMI as a continuous variable in some analyses. In MOND, prepregnancy height and weight were ascertained at the first clinical encounter with an obstetrician, which was objectively measured at the first antenatal visit if prior to 12 weeks gestation and self-reported by the patient otherwise. In the McGill Reproductive clinic, height and weight were self-reported at the time of visit to the fertility specialist and thus predated the index pregnancy. The reproductive clinic data were linked with MOND using unique patient identifiers as well as the date and time of delivery associated with the fertility treatment (to ensure minimal delay between recorded pre-gestational weight and index pregnancy).

While definitions for ART vary slightly, we used the joint Society of Obstetrics and Gynecology and Canadian Fertility and Andrology Society guideline statement definition to encompass all medical treatments involving manipulation of eggs and/or sperm outside the human body, including fresh or frozen IVF with or without ICSI, and IUI, usually following ovarian stimulation therapy. We classified IVF versus spontaneously conceived pregnancies (herein referred to as spontaneous pregnancies) as a binary variable. We also separately evaluated IVF/ICSI versus IUI.

We had data on maternal age, parity, gestational age at delivery (calculated using date of delivery and date of last normal menstrual period (LNMP) or ultrasound dating if LNMP date unknown), use of acetyl-salicylic acid (ASA) during pregnancy (excluding over-the-counter non-steroidal anti-inflammatory use), smoking status during index pregnancy (any versus none), and medical comorbidities including chronic hypertension, diabetes mellitus, renal disease, hypothyroidism, thrombophilia, and polycystic ovarian syndrome (PCOS). Candidate covariates selected for inclusion in the multivariate model were based on substantive and statistical evidence for confounding. Specifically, we conceptualized chronic hypertension, diabetes and PCOS as potential confounders, but also considered the possibility that they represent intermediate steps in the causal pathway between high BMI and preeclampsia. Other medical conditions were carefully considered for inclusion in the model but ultimately excluded either due to small numbers per category with the condition (hypertension, diabetes, renal disease, and thrombophilia), not conceptually true confounders (renal disease and thrombophilia) or to inappropriate classification (hypothyroidism included all biochemical as well as clinically overt cases). Furthermore, we have data on prior events including a history of preeclampsia among multiparous women. However, we recognize that adjustment for prior events risks introducing bias (28), so this was not done in our main analyses.

Statistical analysis

We calculated 95% confidence intervals of the differences in means or proportions between IVF pregnancies with high BMI and spontaneous pregnancies with high BMI. This comparison was to highlight differences in risk factors for preeclampsia other than BMI that may be attributed to IVF. Univariate and multivariate logistic regression were used to evaluate odds of preeclampsia attributed to high BMI and IVF. An interaction term between BMI category and IVF was tested in multivariate models. We considered effect modification to be present if we found a significant interactive effect ($P < 0.20$), heterogeneity across strata of assisted conception, and by computing measures of additive effective modification such as the relative excess risk index (RERI; 29) As an exploratory analysis, we stratified the effect of BMI in IVF versus other ART in an attempt to discern whether there was a treatment effect due to IVF. Results were reported as odds ratios (ORs) and absolute risks (ARs) with 95% confidence intervals. We kept all births from each woman (14.7% of all singleton gestations were repeated pregnancies from the same mother) but corrected for the clustering effect using hierarchical analyses on unique patient identifiers.

We repeated analyses after removing IVF pregnancies using oocyte donors, given its association with hypertension in pregnancy (30). We repeated analyses after removing pregnancies with pre-existing PCOS, hypertension, and diabetes to estimate the direct effect of BMI on preeclampsia risk. We examined the effects of BMI and IVF among nulliparas and multiparas. Multiple imputation was used to handle missing BMI data (58.3% missing from database), and multivariate analyses in the imputed dataset were compared to the un-imputed (complete case) dataset. To address the tendency among women to under-report weight (31), we performed a sensitivity analysis using the bias correction equation based on the 2007-2009 Canadian Health Measures Survey data (32).

This study had a fixed sample size and was powered at 85% to find a 2.5-fold combined effect of BMI $>$ 25 kg/m^2 and IVF on preeclampsia using a two-sided alpha = 0.05 and assuming a baseline incidence of preeclampsia at 5%. Since the sample size required to detect an interactive effect has been estimated to be four-fold the sample size required to find a main effect (33) we considered a conservative threshold (alpha = 0.20) for significance of our product term, as has been suggested by others (34,35). Analyses were conducted using STATA version 12 (StataCorp).

Ethics

The McGill University Health Centre (MUHC) Research Ethics Board approved this study.

Results

Description of study cohort

Our sample included 10,013 singleton pregnancies with complete BMI data; 450 of these were ART pregnancies (IVF, $n = 312$; IVF/ICSI, $n = 36$; IUI, $n = 94$; other/unspecified, $n = 8$) and 9,563 were spontaneous (Figure 1). The mean BMI was 24.6+5.2 kg/m^2 with a symmetric distribution ranging from 15 to 66 kg/m^2, and the distributions of BMI from both data sources (MOND database and reproductive clinic charts) were nearly identical. Approximately one third of the sample had a BMI at least 25 kg/m^2 ($n = 3,614$, 36.1%), and 1,418 (14.2%) were obese. Table 1 shows the characteristics of our

TABLE 1 Maternal and pregnancy characteristics of study cohort stratified by IVF and BMI

	IVF $n = 348$		Spontaneous $n = 9563$	
	n (%) or mean (sd)		n (%) or mean (sd)	
Characteristic	BMI > 25	BMI < 25	BMI > 25	BMI < 25
Subjects	101 (29.0)	247 (71.0)	3,513 (36.3)	6,152 (63.6)
Age (years)[a]	36.6 (4.7)	36.0 (4.4)	32.6 (4.5)	32.0 (4.8)
Nulliparity[a]	81 (80.2)	197 (79.8)	1,317 (37.5)	2,992 (48.6)
Gestational age[b]				
> 37 weeks	90 (89.1)	219 (88.7)	3,197 (91.0)	5,692 (92.5)
34–37 weeks	4 (4.0)	21 (8.5)	218 (6.2)	311 (5.1)
<34 weeks[a]	7 (6.9)	7 (2.8)	98 (2.8)	149 (2.4)
Delivery type				
C-section	37 (36.6)	92 (37.2)	1,313 (37.4)	1,589 (25.8)
Vaginal	64 (63.4)	155 (62.3)	2,200 (62.6)	4,563 (74.2)
Labour induced	42 (41.6)	89 (36.0)	1,211 (34.5)	1,812 (29.4)
Smoking[a]	2 (2.0)	5 (2.0)	224 (6.4)	348 (5.7)
ASA use[a]	24 (23.8)	60 (25.3)	452 (12.9)	565 (9.2)
Medical conditions				
PCOS[a]	16 (15.8)	24 (9.7)	137 (3.9)	142 (2.3)
Hypertension	4 (4.0)	2 (3.3)	126 (3.6)	38 (0.6)
Diabetes	4 (4.0)	6 (2.4)	126 (3.6)	72 (1.2)
Renal disease	1 (1.0)	1 (0.4)	39 (1.1)	52 (0.8)
Thrombophilia	3 (2.9)	11 (4.4)	79 (2.2)	85 (1.4)

Abbreviations: IVF: *in vitro* fertilization; BMI: body mass index in kg/m^2; PCOS: polycystic ovarian syndrome; ASA: acetyl-salicylic acid.
[a]Indicates significant difference between high-BMI IVF and high-BMI spontaneous at alpha = 0.05 (95% CI of the difference not crossing the null value).
[b]Gestational age at delivery, calculated using date of delivery and date of last normal menstrual period (LNMP) or ultrasound dating if LNMP date unknown.

cohort, stratified by IVF status and BMI category. Overweight and obese women conceiving through IVF were older, more likely to be nulliparous, and more likely to have PCOS than spontaneously conceived. Early preterm delivery (prior to 34 weeks) occurred in 7 (6.9%) of those with high BMI treated with IVF, 5 of which were by c-section and 2 of which were induced vaginal deliveries. About one fifth of the IVF group took ASA during pregnancy, reflecting obstetric practices in our center to reduce preeclampsia among high-risk women.

Preeclampsia occurred in 1,006 (4.2 %) pregnancies overall and in 512 (5.1%) of the sample with complete BMI data. The majority of preeclampsia cases were nonsevere: very few had concomitant HELLP ($n = 29$, 2.9%) or eclampsia ($n = 2$, 0.2%), and proportionally few delivered before 34 weeks ($n = 102$, 10.1%). Among preterm preeclampsia, abruptio placentae was rare ($n = 7/223$, 3.1%). Among multiparous preeclampsia cases, about one third had prior preeclampsia (118/400, 29.5%). A substantial proportion used ASA during pregnancy ($n = 126$, 12.5 %).

Association between high BMI and preeclampsia

The factors significantly associated with preeclampsia in univariate analyses included BMI, ART, IUI, maternal age 40 years or older, nulliparity, as well as medical conditions preceding pregnancy, including chronic hypertension, diabetes mellitus, renal disease, and PCOS (Table 2).

High BMI retained significance in multivariate analyses adjusted for age, parity, PCOS, ASA use, and IVF. Overweight and obese women were 3 times more likely to experience preeclampsia than those with normal BMI (adjusted OR 3.4, 95% CI 2.8-4.2), which was similar among obese only. For every unit increase in BMI, we observed a 10% increase in the risk of preeclampsia (adjusted OR 1.11, 95% CI 1.09-1.12). Conversely, we found no effect of IVF on odds of preeclampsia in multivariate analyses (OR 0.6, 95% CI 0.3-1.4; Table 3).

Combined effects of ART and high BMI on preeclampsia risk

Table 3 presents adjusted individual and combined effects of IVF and high BMI at both BMI cutoffs. Women with a BMI > 25 kg/m^2 conceiving through IVF were 4.5 times more likely to develop preeclampsia (OR 4.6, 95% CI 2.8-8.1) compared with nonoverweight women who conceived spontaneously. An IVF pregnancy in an obese mother was nearly seven times more likely to be complicated by preeclampsia (OR 6.7, 95% CI 3.3-13.8) compared with spontaneous nonobese pregnancies. There was evidence for departure from multiplicativity (P-value 0.13 and 0.03 for interaction term with IVF at BMI > 25 kg/m^2 and BMI > 30 kg/m^2, respectively; Table 3).

ARs (95% CI) were derived from the regression model for each level of exposure: 1.8% (0.4-3.2) for IVF treated pregnancies with

TABLE 2 Unadjusted associations with preeclampsia

Characteristic	OR (95% CI)	*P*-value	Preeclampsia cases, $n = 512$ *N* with/without specific characteristic
BMI (per kg/m^2)	1.10 (1.08-1.12)	<0.001	N/A
BMI > 25 (kg/m^2)	3.2 (2.7-3.9)	<0.001	324/188
BMI > 30 (kg/m^2)	3.5 (2.9-4.3)	<0.001	178/334
ART (any)[a]	1.4 (1.0-2.1)	0.05	32/480
IVF/ICSI	1.3 (0.8-2.0)	0.30	22/490
IUI	2.3 (1.2-4.3)	0.01	10/480
Age, per 1 y	1.0 (0.99-1.01)	0.87	N/A
Age, > 40 y	1.5 (1.1-2.0)	0.008	51/461
Nulliparity	2.0 (1.7-2.4)	<0.001	318/194
Medical conditions			
PCOS	1.8 (1.2-2.6)	0.006	27/485
Hypertension	12.7 (9.0-17.7)	<0.001	64/448
Diabetes	3.8 (2.5-5.7)	<0.001	34/478
Renal Disease	2.3 (1.2-4.4)	0.02	10/502
Thrombophilia	1.1 (0.6-2.1)	0.76	10/502

Abbreviations: OR: odds ratio; CI: confidence interval; BMI: body mass index; ART: assisted reproductive technology; IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection; IUI: intrauterine sperm insemination; y: year(s); PCOS: polycystic ovarian syndrome.
Odds ratios denote the crude odds of preeclampsia in women with each condition, as compared to without each condition.
Right-hand column gives raw numbers of preeclampsia cases with and without each condition.
[a]Reference category for ART and subtypes is spontaneously conceived birth.

low maternal BMI; 2.9% (2.5-3.3) for spontaneous pregnancies with low BMI; 9.2% (8.3-10.3) for spontaneous pregnancies with maternal BMI > 25 kg/m^2; and 11.9% (95% CI 6.3-17.6) for both IVF and maternal BMI > 25 kg/m^2. The AR of preeclampsia in an obese woman pregnant through IVF was 21.1% (9.6-32.6). Since our predefined reference category (spontaneous low BMI) was not at the lowest risk of the outcome, we did not compute measures of additive effect modification such as the RERI, as this estimate would be invalid (36). However, visual inspection demonstrated divergence of AR, particularly at higher BMI (Figure 2).

The effect of high BMI on preeclampsia risk was more pronounced in IVF versus other ART pregnancies (mostly IUI; OR 2.0, 95% CI 0.6-7.0 for IUI group; OR 7.5, 2.8-20.0 for IVF group) after adjusting for age and parity, although numbers in strata were small.

Sensitivity analyses

We found similar trends in subgroup analyses removing IVF pregnancies using oocyte donors ($n = 25$), with chronic hypertension ($n = 170$), diabetes mellitus ($n = 208$), PCOS ($n = 319$), and among nulliparas ($n = 4{,}587$; Appendix, Table A1). Among multiparas ($n = 5{,}426$), prior preeclampsia strongly predicted the outcome (OR 3.7, 95% CI 2.6-5.4).

When imputing missing prenatal BMI in multivariate linear regression, we estimated an average of 41.0% of the sample with a BMI at least 25 kg/m^2 and 13.8% with BMI at least 30 kg/m^2 compared with 36.1% and 14.2%, respectively, in the complete-case cohort. We observed similar trends in our analyses of imputed data, with higher effects due to BMI in the presence of IVF. (Appendix, Table A2)

After correcting for self-reported weight bias: $[-0.12 + (1.05) \times \text{BMI}]$ (32), the estimated combined effect of IVF and BMI > 25 kg/m^2 was slightly lower than previous estimates (OR 3.7, 95% CI 2.2-6.4), but still higher than individual effects of BMI or IVF, and evidence for synergism persisted (*P*-value for interaction with IVF: 0.12).

Discussion

In this hospital-based cohort study, we found that when compared with normal-weight pregnancies, being overweight or obese conferred a high risk of preeclampsia that was further compounded by IVF. IVF did not independently increase one's risk of preeclampsia. In fact, IVF pregnancies in the presence of low-normal maternal BMI experienced a low AR of preeclampsia (~2%), while IVF pregnancies in the presence of a high BMI experienced a high AR of preeclampsia (~12%). Heterogeneity of the relative effect of BMI on preeclampsia across strata of IVF treatment and significant interactive effects (particular among obese) together suggest that a

TABLE 3 Modification of the effect of high BMI on preeclampsia risk by IVF status

	Spontaneous		IVF				
	N with/without preeclampsia	OR (95% CI)	*N* with/without preeclampsia	OR (95% CI)	*P*[a]	OR (95% CI) for BMI within strata of IVF	
BMI < 25	182/5,970	**1.0 (ref)**	6/241	0.6 (0.3-1.4)	N/A	**No IVF**	**IVF**
BMI > 25	308/3,205	3.4 (2.8-4.2)	16/85	4.6 (2.8-8.1)	0.12	3.4 (2.8-4.2)	7.3 (2.6-20.9)
BMI > 30	167/1,212	3.6 (2.9-4.4)	11/28	6.7 (3.3-13.8)	0.03	3.6 (2.9-4.4)	9.5 (3.6-25.5)

Abbreviations: OR: odds ratio; CI: confidence interval; BMI: body mass index (kg/m^2); IVF: *in vitro* fertilization; PCOS: polycystic ovarian syndrome.
ORs for individual and combined effects of IVF and high BMI compared with neither factor (reference), adjusted for age, parity, aspirin use during pregnancy, and PCOS. On far right, ORs and 95% CI are within strata of IVF, adjusted for age, parity, PCOS, and aspirin use.
[a]*P*-value for interaction between high BMI and IVF (significance at alpha = 0.20).

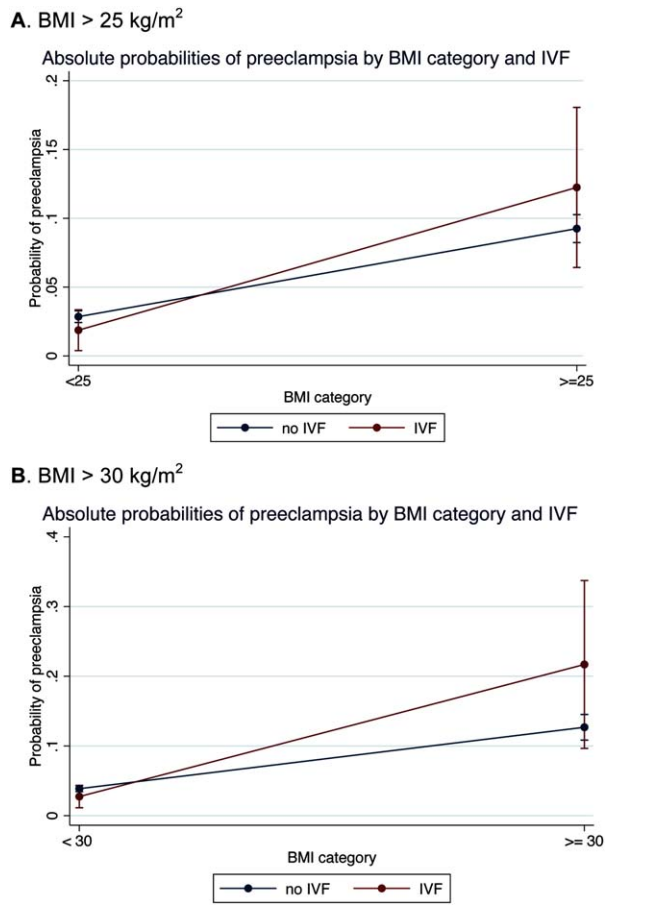

Figure 2 Absolute effect of high BMI on preeclampsia risk by IVF status at two BMI cutoffs. (**A**) BMI > 25 kg/m^2. (**B**) BMI > 30 kg/m^2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

high BMI interacts with IVF, although we were unable to confirm additive effect modification using the RERI.

The incidence of preeclampsia in this cohort approximated usual reported incidence (19). Our findings are comparable with previous studies showing a 3-fold increased risk of preeclampsia among overweight and obese pregnant women (14,16,17). The possibility that adverse pregnancy outcomes in IVF pregnancies are explained by confounders including multiple gestation, age, parity, and infertility, has been previously suggested (23). We excluded multiples, and adjusted for age and parity in multivariate analyses. We also adjusted for PCOS because of its established associations with high BMI, and preeclampsia (37).

The combination of both high BMI and IVF appeared particularly detrimental. One possible explanation for this finding is that higher doses of gonadotropins are required to achieve conception in overweight and obese women who undergo IVF (11,38). Aggressive superovulation protocols may alter the endometrial lining and impair subsequent placentation, leading to the preeclampsia syndrome. Furthermore, embryonic implantation may activate the maternal immune response, exacerbating the inflammatory state described in obese pregnancies characterized by increased levels of circulating cytokines (39). Finally, high BMI may interact with an infertility factor, and IVF treatment may be a surrogate for this putative factor. Whether or not the effect is due to treatment, implications are that careful consideration of ART is required in women with high BMI.

Several aspects of our study are novel. Although numerous studies have reported increased preeclampsia risk in women with high BMI (14-17) or compared obese and nonobese IVF pregnancies with regard to clinical IVF outcomes (12,40), to our knowledge this is the first study to specifically assess preeclampsia risk due to the combined effect of high BMI and IVF conception. We assessed the potential for effect modification of high BMI on preeclampsia by IVF. We used a large hospital-based clinical database that has collected obstetric and neonatal data since 1978, and ART data since 2001. Furthermore, we adjusted for important known confounders in multivariate analyses and performed analyses to adjust for bias due to misclassification and missing data. Finally, we reported ARs in addition to relative measures of effect.

Our study has limitations. The high proportion of missing BMI data in the MOND database was of concern, and necessitated further analysis. However we believe that our complete case analysis was representative of the MOND cohort. First, height and weight were derived in a busy antenatal clinic, where missingness is likely random. Furthermore, our main results were effectively unchanged after multiple imputation. Finally, our cohort had similar proportions of overweight and obese pregnancies as a recent randomized Australian study with nearly 90% complete BMI information at first antenatal visit (16).

We addressed the possibility of bias due to self-reported weight, which was likely minimal and nondifferential. Misclassification due to self-report is independent of the outcome since women reported their weights prior to the occurrence of preeclampsia, and independent of conception method, since women reported their weight knowing that it will be objectively measured. Furthermore, results were similar after bias correction for self-reported weight (32).

We lacked information on hormonal stimulation protocols. However, after excluding donor oocyte pregnancies in a sensitivity analysis, results were unchanged.

Our data spanned from 2001 until 2008. Temporal trends may affect interpretation of our results. Standard definitions for obesity and preeclampsia were unchanged during the study period. However, Quebec policy mandating public funding of ART in 2010 has changed the demographic of the ART-treated population (8). Socio-economic differences in the current versus study population cannot be excluded.

While our results are hypothesis generating, they have important potential implications. In areas where fertility treatments are publicly funded, there has been a tendency to restrict access to IVF to women with BMI below arbitrary thresholds, based largely on inconclusive data suggesting reduced success rates in obese women. Information is needed not only on live birth rates in overweight and obese women who use IVF, but also on the occurrence and risk of pregnancy complications. Preeclampsia is one of the most frequent pregnancy complications worldwide and has potential serious morbidity to mother and offspring. Weight loss recommendations to achieve a normal BMI should continue to be strongly encouraged

prior to IVF, not only to increase one's chances of successful pregnancy, but also to mitigate preeclampsia risk. In conjunction with lifestyle strategies, policies that restrict IVF access based on BMI may be necessary to prevent excess risks of serious complications such as preeclampsia. In the context of increasing availability of and demand for ART, more attention should be focused on the effects of ART on maternal health. Efforts are needed to identify those women at high risk for serious complications, and to assess whether morbidity during pregnancy is enhanced due to ART. O

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