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GESTATIONAL HYPERTENSION IN PREGNANCIES SUPPORTED BY INFERTILITY TREATMENTS. ROLE OF INFERTILITY, TREATMENTS, AND MULTIPLE GESTATIONS

Sonia Hernández-Díaz, M.D., Dr.P.H.[a,b], **Martha M. Werler, Sc.D.**[a], and **Allen A. Mitchell, M.D.**[a]

a *Slone Epidemiology Center at Boston University, Boston, MA*

b *Department of Epidemiology, Harvard School of Public Health, Boston, MA*

Abstract

Objective—To investigate the association between infertility treatments and gestational hypertension and preeclampsia.

Design—Retrospective observational cohort.

Setting—General population, United States and Canada.

Patients—5151 women with non-malformed infants participating in the Slone Epidemiology Center Birth Defects Study between 1998 and 2006.

Interventions—Women were interviewed within six months after delivery about sociodemographic and medical factors, the onset of gestational hypertension and preeclampsia, and about infertility treatments.

Main Outcome Measures—We estimated relative risks and 95% confidence intervals using unconditional logistic regression.

Results—The incidence of gestational hypertension was 8.9% (423/4762) among women without infertility treatments, and 15.8% (55/349) among women undergoing infertility treatments. Compared to spontaneous pregnancies, the crude relative risk for gestational hypertension in pregnancies resulting from infertility treatments was 1.9 (95% confidence interval 1.4–2.6). Multivariate adjustment for parity and pre-pregnancy BMI resulted in a relative risk of 1.6 (1.1–2.1). Further adjustment for multiple pregnancies, or restriction of the analyses to singleton pregnancies, moved the relative risk to 1.3. Each specific infertility procedure or drug was associated with a similarly elevated risk, which disappeared after adjustment for multiple gestations. Results were similar for preeclampsia.

Corresponding Author: Allen A. Mitchell, M.D., Slone Epidemiology Center, Boston University, 1010 Commonwealth Avenue, Boston, MA 02215, USA, Tel: (617) 734 6006, Fax: (617) 738 5119, e-mail: E-mail: amitchell@slone.bu.edu.

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CAPSULE: The higher incidence of gestational hypertension and preeclampsia in pregnancies resulting from infertility treatments is largely explained by the higher frequency of multiple gestations.

Conclusion—Pregnancies resulting from infertility treatments have a higher incidence of gestational hypertension and preeclampsia than spontaneous conceptions. This increased risk is largely explained by the higher frequency of multiple gestations.

Keywords

preeclampsia; hypertension; pregnancy; infertility; fertility treatments

INTRODUCTION

Preeclampsia, clinically recognized by gestational hypertension with proteinuria, is a leading cause of maternal and perinatal morbidity and mortality. Although it is widely accepted that the disorder starts with defective implantation, the ultimate causes are still unclear.(1) Among other mechanisms, it has been proposed that preeclampsia is the consequence of a maternal immune reaction against paternal antigens expressed in the placenta,(2) and that this reaction might result in defective trophoblast invasion and subsequent placental dysfunction.(3) It has also been proposed that prolonged exposure and adaptation to antigenic factors on the spermatozoa or on the placenta (i.e., “desensitization”) might have a protective effect.(4,5)

An exaggerated maternal immune reaction may not only result in defective implantation but might also eliminate the implanting conceptus.(3) That is, preeclampsia and implantation disorders might share etiologic pathways, including those involving immunological functions.(2) In fact, fertility difficulties have been associated with a higher risk of gestational hypertension and preeclampsia.(6–8) Thus, it has been suggested that elevated risks of preeclampsia observed in women treated for infertility(9,10) stem from the underlying disorder rather than from the infertility treatments themselves.

Yet, an independent and direct effect of fertility treatments remains a plausible explanation for the elevated risk of gestational hypertension and preeclampsia in pregnancies resulting from such treatments compared to spontaneous ones. For example, intracytoplasmatic sperm injection in couples where the number of sperm cells available during intercourse is negligible,(11) or intrauterine insemination with donor sperm, oocytes or embryos,(4,12,13) might increase the risk by triggering an immune reaction in women without prior desensitization. Unfortunately, early studies on this subject were based on relatively small series of patients without appropriate control for age and parity; they also failed to consider the higher prevalence of multiple gestations resulting from assisted reproduction, an important factor since multiple gestations themselves carry a higher risk of preeclampsia.(14,15) Among the more recent studies that adjusted for maternal age and parity and considered multiple gestations, some have found an increased risk in women receiving infertility treatments, even after stratification for number of fetuses,(16,17) or restriction to singletons(8,18–21) or multiple gestations.(22,23) Others have found no significant differences between assisted and spontaneous pregnancies after stratification,(24) or restriction to singletons(25–29) or multiple gestations.(29–34)

It thus remains unclear whether the association between infertility treatments and gestational hypertension is due to biologic factors intrinsic to couples with infertility problems, to patient characteristics such as older age and primiparity, to the higher rate of multiple gestations, or to the specific infertility treatment. We therefore investigated the association between fertility treatments and gestational hypertension, with specific emphasis on the effect of different technologies and specific fertility drugs, as well as the role of multiple gestations and specific patient characteristics.

MATERIALS AND METHODS

Study Population

As part of an on-going case-control surveillance program of birth defects (the Slone Epidemiology Center Birth Defects Study), non-malformed newborns were ascertained at birth and tertiary care hospitals in the greater metropolitan areas of Boston, Philadelphia, Toronto, and San Diego, including a population-based sample of Massachusetts births.(35) The study population for the current analysis comprised 5274 mothers of non-malformed infants ascertained between 1998 and 2006. Institutional Review Board approval was obtained from each of the participating institutions. All mothers who were interviewed gave oral or written consent. The participation rate was 68%. After exclusion of mothers who could not be located and invited to participate, the rate was 71%.

Assessment of Exposure

Within six months of delivery, trained study nurses who were unaware of the hypothesis interviewed the mothers by telephone. The interview included questions on demographic characteristics, the mother's medical and obstetrical history, parents' habits and occupations, and a detailed history of the use of medications (prescription and non-prescription) from two months before conception through the entire pregnancy. Specific questions focused on pregnancy planning, history of fertility problems, and infertility procedures or medications used by the women or their partners in the index pregnancy. We considered mothers to be exposed if, to assist the index pregnancy, they reported using ovulation induction (including clomiphene citrate, human menopausal gonadotropins [hMG], chorionic gonadotropin, or follicle stimulating hormone), intrauterine insemination (IUI), or assisted reproductive technologies (ART) (including in vitro fertilization [IVF], intracytoplasmatic sperm injection [ICSI], or gamete intrafallopian transfer [GIFT]). The reference group included women without fertility treatments.

Outcome

We specifically asked women if a health care provider had diagnosed "high blood pressure" or "toxemia or preeclampsia" during their pregnancy, the dates when the condition started and ended, and whether they had used medications to treat those conditions. To exclude underlying hypertension as a potential source of both confounding and outcome misclassification bias, we restricted the definition of gestational hypertension to hypertension (with or without preeclampsia) diagnosed after the 20^{th} week of pregnancy; we excluded 123 women with an early diagnosis of hypertension from all the analyses. Preeclampsia was defined as self-reported "toxemia" or "preeclampsia".

Data Analysis

We considered our population as a retrospective cohort of women with completed pregnancies. Relative risks (RR) and 95 percent confidence intervals (95% CI) were estimated for gestational hypertension and preeclampsia in relation to infertility treatments using logistic regression models. To identify potential confounders, we considered the following factors: gravidity, parity, age, pre-pregnancy weight and body mass index (BMI), smoking, coffee intake, age at menarche, education, family income, race, and diabetes;(36) we retained in the models as potential confounders those factors independently associated with the outcome in our population. In addition, we considered carrying a multiple pregnancy as a potential intermediate variable in the etiologic pathway between infertility treatments and gestational hypertension or preeclampsia. Forty women with missing data for the fertility questions were excluded from the fertility analyses.

RESULTS

Of 5151 women, 480 (9.3%) reported gestational hypertension and 133 (2.6%) preeclampsia. The women's baseline characteristics are shown in table 1. Factors associated with both gestational hypertension and preeclampsia were primiparity, higher pre-pregnancy weight, early menarche, and multiple gestations.

Women who conceived after infertility treatments were more likely to be over 35 years of age, white and primiparous, and to have a history of miscarriages, high education and high income levels; they were less likely to be underweight and to smoke or drink coffee during pregnancy than women who conceived spontaneously (data not shown). Pregnancies assisted by infertility treatments had a much higher frequency of multiple gestations (23%) than spontaneous pregnancies (1.7%). The proportion of preterm deliveries (<37 weeks) was 17.5% in women undergoing fertility treatments and 6.6% in women with no fertility disorder.

Table 2 presents crude and adjusted relative risks for gestational hypertension. The incidence of gestational hypertension was higher among women with treated fertility problems (15.8 %) than among those who did not receive such treatments (8.9%); compared to the last group, the crude RR for gestational hypertension for women with treated fertility problems was 1.9 (95% CI 1.4–2.6). Upon adjustment for parity and pre-pregnancy BMI (the only factors that acted as confounders), the RR changed to 1.6 (95% CI 1.1–2.2). After adjustment for twins and higher order gestations, the RR for infertility treatments went from 1.6 to 1.3 (95% CI 1.0–1.9). Restriction of the analysis to singleton pregnancies yielded an adjusted RR of 1.3 (95% CI 0.9–1.9), and the adjusted RR was 1.1 (95% CI 0.4–3.1) among twins.

The frequency of multiple gestations varied among infertility procedures (5.6% for ovarian stimulation only, 19.3% for intrauterine insemination, and 47.2% for assisted reproductive techniques) and among medications (6.7% for clomiphene without infertility procedures, 21.8% for clomiphene with additional infertility procedures, 36.3% for gonadotropins, and 41.9% for follicle stimulating hormones). As shown in Table 3, those treatments associated with the highest proportions of multiple gestations were associated with an elevated risk of gestational hypertension. When estimates were further adjusted for multiple gestations, RRs across all treatments approached the null.

As shown in Table 4, the risk of preeclampsia was higher (5.2%) among women with treated infertility than among those who did not require treatments (2.4%). The crude RR for preeclampsia for women with treated infertility was 2.2 (95% CI 1.3–3.7), compared to women without infertility treatments. Adjustment for other risk factors reduced the RR to 1.6 (95% CI 1.0–2.7), and further adjustment for multiple gestations reduced it to 1.2 (95% CI 0.7–2.2). Results from more specific analyses for preeclampsia were similar to those presented above for gestational hypertension, but the numbers were smaller and the estimates were more unstable.

The unadjusted RRs of both gestational hypertension and preeclampsia were elevated for procedures with and without donor sperm or oocytes and with or without concomitant ovarian stimulation. The estimates for these comparisons were statistically unstable given the relatively small sample sizes and are not shown. Within the group of women without infertility treatments, those who reported fertility problems in the past or untreated sub-fertility in the index pregnancy did not have an elevated risk. Results were similar for primiparous and multiparous women and did not change when we analyzed the data using time to event analysis (i.e., Cox proportional hazard models), nor upon restriction of the analysis to full term births or to the population-based sample recruited from Massachusetts, nor when using frequency matching for region and calendar year through conditional logistic regression.

DISCUSSION

We found a higher frequency of gestational hypertension and preeclampsia in pregnancies resulting from infertility treatments than in spontaneous pregnancies. This increased risk was partially explained by the specific characteristics of the women undergoing infertility treatments, mainly primiparity and higher pre-pregnancy BMI, and the remaining association disappeared when the analysis was restricted to singletons. Results were similar for all infertility procedures and medications upon adjustment for multiple gestations. Neither past sub-fertility nor untreated sub-fertility in the index pregnancy was associated with gestational hypertension.

Our results are consistent with previous studies that found no significant differences between assisted and spontaneous pregnancies after adjusting for multiple gestations or restricting the analyses to singletons or twins.(24–29) These findings suggest that the elevated risk of gestational hypertension and preeclampsia in pregnancies resulting from infertility treatments is related to their higher proportion of twins and higher order gestations. However, controlling for multiple gestations would be unwarranted if the goal were to estimate the total impact of infertility treatments on the risk of gestational hypertension, whether or not this effect is mediated through multiple gestations. On the other hand, controlling for multiple gestations would be necessary to assess the direct effects of infertility treatments on gestational hypertension, independently of their effects on increasing multiple gestations.(37,38) While the total effect of infertility treatments might be of greater interest from a public health point of view; advancing insight into the role of multiple gestations contributes to our understanding of gestational hypertension and preeclampsia. Moreover, from a clinical perspective, it is useful for those contemplating infertility procedures to know whether their risks of gestational hypertension and preeclampsia are increased by the intervention (e.g., ART) or the multiple gestations, since the former may be difficult to avoid but the latter might be reduced (e.g., by implanting fewer embryos).

Regarding the role of specific treatments, some studies have suggested a particularly elevated risk of preeclampsia associated with ICSI and gamete donation,(4,11–13) while others found similar risks for different reproductive procedures, including IVF, GIFT, and ovulation induction.(20,21,33,39) Our findings are consistent with the latter studies and suggest that the apparent differences among technologies might be largely explained by different rates of multiple gestations associated with them. However, due to the relatively small sample size, the risk estimates for specific treatments were unstable and did not exclude modest differences among treatments.

It has been suggested that the association between infertility treatments and gestational hypertension stems from an underlying disorder, such as immune maladaptation, that would increase the risk of both infertility and preeclampsia.(2) Our results are inconsistent with this hypothesis since neither past sub-fertility nor untreated sub-fertility in the index pregnancy was associated with gestational hypertension, and the elevated risk associated with treated infertility was largely explained by primiparity, higher weight, and the increased number of multiple gestations. Unfortunately, our study lacked information on the specific etiology of infertility and, therefore, we were not able to evaluate the risk of gestational hypertension among specific populations of infertile patients who might have an inherently increased risk.

The discrepant findings among previous publications might derive not only from the way those studies dealt with twins and higher order gestations but from other methodological differences. For instance, some of the positive studies that relied on records in automated medical databases considered only gestational hypertension requiring hospitalization. This outcome definition may be prone to bias if there were a lower threshold for hospitalization among women who

conceive as a result of assisted reproduction. In addition to this potential source of bias, studies that compared infertility cohorts with outcome rates from the general population would tend to overestimate the risk of infertility treatments due to both a better recording of diagnosis in *ad hoc* cohorts and the specific characteristics of women with infertility (e.g., primiparous).

Since we did not have access to obstetric notes in mothers' medical records, our reliance on self-reported outcome information may include under-reporting of events and cross-classification of preeclampsia as gestational hypertension. However, such misclassification is likely to have been minimized by use of a carefully designed questionnaire that included specific questions on the onset of gestational hypertension and preeclampsia as diagnosed by a health care provider; in addition, interviews were conducted within six months of delivery by trained nurses who were unaware of the hypothesis under study. Under-diagnosis is unlikely since over 99 percent of the women in our population had had prenatal care, where screening for the detection of gestational hypertension and proteinuria is standard practice. Moreover, results were similar within levels of women's education (i.e., if diagnosis, awareness, or recall were poor, one might expect more misclassification among women with lower education).

Further, the data offer evidence of the general validity of the outcome definitions: First, the reported incidence of gestational hypertension with or without preeclampsia (12.4%) and the incidence of preeclampsia (5.3%) among primiparous women in our population are similar to those described in clinical trials.(40) Second, the frequency and effect of other known risk factors (e.g., gravidity, number of fetuses, and maternal weight) are similar to those consistently reported in the literature,(41) and the associations with coffee intake and early menarche were also described in two previous publications.(42,43) Other previously suggested risk factors, such as advanced maternal age, diabetes, and Black race, were not associated with a higher frequency of gestational hypertension in our study; most likely because we excluded women with chronic hypertension (i.e., these factors were associated with hypertension diagnosed before 20 weeks of gestation). Our failure to find the previously suggested protective effect of smoking(44) might be due to differences among populations, methodological factors, or/and chance.

More directly, we evaluated the susceptibility of the results to outcome misclassification.(45) For both gestational hypertension and preeclampsia, the sensitivity of interview data ranges from 65% to 100% (estimated as recall against medical record).(46,47) Were misclassification to occur similarly among women with and without fertility treatments, such bias would result in a slight underestimation of the effect of infertility treatments. For example, assuming a sensitivity of 65% (i.e., 35% of women with preeclampsia failed to report it), the corrected crude RR for preeclampsia would have been 2.24 rather than 2.20. On the other hand, if gestational hypertension were diagnosed more readily among women undergoing assisted reproduction (e.g., due to a more intensive antenatal care), such bias would result in an overestimation of the infertility treatment effects; that is, the adjusted unbiased effect would be even closer to the null than the observed one.

In conclusion, we found that pregnancies resulting from infertility treatments have a slightly higher risk of gestational hypertension than spontaneous conceptions in women of comparable parity and weight. However, this increased risk appears to be largely attributable to the higher frequency of twins and higher order gestations resulting from infertility treatments, since multiple gestations themselves carry a higher risk of gestational hypertension.

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Table 1

Incidence of gestational hypertension and preeclampsia according to women's characteristics.

Women's characteristics	Total[a] N=5151	Gestational hypertension		Preeclampsia	
	No.	No. (%)	RR (95%CI)[b]	No. (%)	RR (95%CI)[b]
		Gravidity			
Primigravidae (first gestation)	1601	196 (12.4)	Reference	60 (3.8)	Reference
Multigravidae					
Primiparous (first liveborn)	613	85 (13.9)	1.1 (0.8–1.4)	33 (5.4)	1.3 (0.9–2.1)
Multiparous	2937	199 (6.8)	0.5 (0.4–0.6)	40 (1.4)	0.3 (0.2–0.5)
Interpregnancy interval ≤3y	2142	132 (6.2)	0.4 (0.3–0.6)	28 (1.3)	0.3 (0.2–0.5)
Interpregnancy interval >3y	767	64 (8.3)	0.6 (0.4–0.8)	12 (1.6)	0.4 (0.2–0.7)
Number of fetuses					
Single	4986	448 (9.0)	Reference	120 (2.4)	Reference
Multiple (2 or more)	165	32 (19.4)	1.9 (1.2–2.9)	13 (7.9)	2.5 (1.4–4.8)
Twins	143	24 (16.8)	1.7 (1.0–2.6)	10 (7.0)	2.3 (1.2–4.7)
Triplets	22	8 (36.4)	4.6 (1.8–11.4)	3 (13.6)	4.8 (1.3–17.4)
Pre-pregnancy weight (lbs)					
<120	1224	73 (6.0)	Reference	21 (1.7)	Reference
120–135	1391	91 (6.5)	1.1 (0.8–1.5)	26 (1.9)	1.1 (0.6–1.9)
135–150	1054	110 (10.4)	1.8 (1.3–2.5)	38 (3.6)	2.0 (1.2–3.5)
>150	1435	197 (13.7)	2.5 (1.9–3.4)	45 (3.1)	1.7 (1.0–3.0)
Maternal BMI [c]					
<20	848	47 (5.5)	Reference	17 (2.0)	Reference
20–27	3213	275 (8.6)	1.7 (1.2–2.3)	82 (2.6)	1.3 (0.7–2.2)
>27	1011	148 (14.6)	3.1 (2.2–4.4)	30 (3.0)	1.4 (0.8–2.6)
Diabetes					
No	4919	452 (9.2)	Reference	122 (2.5)	Reference
Yes	232	28 (12.1)	1.3 (0.8–1.9)	11 (4.7)	1.8 (0.9–3.5)
Smokers					
Never	2995	266 (8.9)	Reference	64(2.1)	Reference
Before pregnancy	1279	119 (9.3)	1.0 (0.8–1.3)	37(2.9)	1.3 (0.8–1.9)
During pregnancy	875	95 (10.9)	1.1 (0.8–1.5)	32(3.7)	1.6 (1.0–2.6)

Women's characteristics	Total[a] N=5151	Gestational hypertension		Preeclampsia	
	No.	No. (%)	RR (95%CI)[b]	No. (%)	RR (95%CI)[b]
Coffee					
Never	2430	232 (9.6)	Reference	56 (2.4)	Reference
Before pregnancy	2002	167 (8.3)	0.9 (0.7–1.1)	47 (2.4)	0.9 (0.6–1.4)
During pregnancy	719	81 (11.3)	1.3 (1.0–1.7)	27 (3.8)	1.7 (1.0–2.7)
Race					
White	3777	378 (10.0)	Reference	109 (2.9)	Reference
Black	348	32 (9.2)	0.8 (0.5–1.3)	8 (2.3)	0.9 (0.4–1.9)
Other	1025	70 (6.8)	0.7 (0.5–0.9)	16 (1.6)	0.5 (0.3–1.0)
Menarche					
<12	913	111 (12.2)	1.4 (1.1–1.7)	36 (3.9)	1.8 (1.2–2.7)
>=12	4059	356 (8.8)	Reference	91 (2.2)	Reference
Maternal Age					
<25 years	1162	119 (10.2)	Reference	35 (3.0)	Reference
25–30 years	1400	134 (9.6)	1.0 (0.7–1.3)	36 (2.6)	0.9 (0.5–1.6)
31–35 years	1761	149 (8.5)	0.9 (0.7–1.3)	43 (2.4)	1.0 (0.5–1.8)
>35 years	814	78 (9.6)	1.0 (0.7–1.5)	19 (2.3)	0.9 (0.4–1.7)
Education					
<13 years	1389	133 (9.6)	Reference	34 (2.5)	Reference
13–15	1260	105 (8.3)	0.9 (0.6–1.2)	30 (2.4)	1.2 (0.7–2.1)
>15 years	2499	242 (9.7)	1.1 (0.8–1.4)	69 (2.8)	1.5 (0.9–2.6)
Family Income ($/year)					
<45,000	1418	142 (10.0)	Reference	39 (2.8)	Reference
>45,000	3305	306 (9.3)	0.9 (0.7–1.1)	84 (2.5)	0.8 (0.5–1.2)
Unknown	428	32 (7.5)	0.7 (0.5–1.1)	10 (2.3)	0.9 (0.4–1.8)

RR: Relative risk. 95%CI: 95 percent confidence interval.

[a] Due to missing values not all the variables contained information on 5024 women. Independent categories were created for women with missing values.

[b] Adjusted for the other variables in the table and geographic region.

[c] BMI denotes Body Mass Index (kg/cm^2). Data missing because some women did not report their height.

Table 2

Incidence of gestational hypertension according to women's infertility history and accounting for multiple gestations.

		Gestational hypertension			
	Total No.	**Incidence No. (%)**	**Model 1 Crude RR (95% CI)**	**Model 2 [a] Adjusted RR (95% CI)**	**Model 3 [b] Adjusted RR (95% CI)**
Overall (N=5111)					
Fertility treatment					
No	4762	423 (8.9)	Reference	Reference	Reference
Yes	349	55 (15.8)	1.9 (1.4–2.6)	1.6 (1.1–2.1)	1.3 (1.0–1.9)
Singleton gestation (N=4947)					
Fertility treatment					
No	4680	413 (8.8)	Reference	Reference	NA
Yes	267	34 (12.7)	1.5 (1.0–2.2)	1.3 (0.9–1.9)	
Twins (N=142)					
Fertility treatment					
No	76	10 (13.2)	Reference	Reference	NA
Yes	66	13 (19.7)	1.6 (0.7–4.0)	1.1 (0.4–3.1)	

RR: Relative risk. 95%CI: 95 percent confidence interval.

[a] Adjusted for pre-pregnancy BMI and parity.

[b] Adjusted also for number of fetuses

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Table 3

Incidence of gestational hypertension according to women's specific infertility treatment.

Women's characteristics	Total N=5111	Gestational hypertension			
	No.	No. (%)	Crude RR (95%CI)	Adjusted RR (95%CI) [a]	Adjusted RR (95%CI) [b]
Fertility treatment					
No	4762	423 (8.9)	Reference	Reference	Reference
Specific treatments					
Drugs only	105	14 (13.3)	1.6 (0.9–2.8)	1.4 (0.8–2.5)	1.3 (0.7–2.3)
IUI	83	14 (16.9)	2.1 (1.2–3.7)	1.6 (0.9–2.9)	1.4 (0.8–2.6)
ART	124	20 (16.1)	2.0 (1.2–3.2)	1.6 (1.0–2.7)	1.2 (0.7–2.1)
Others	37	7 (18.9)	2.4 (1.0–5.5)	1.8 (0.8–4.3)	1.8 (0.8–4.3)
Specific drugs [c]					
Clomiphene	129	24 (18.6)	2.3 (1.4–3.6)	1.9 (1.2–3.0)	1.7 (1.0–2.7)
Without procedures	74	10 (13.5)	1.6 (0.8–3.1)	1.4 (0.7–2.7)	1.3 (0.6–2.5)
With procedures	55	14 (25.5)	3.4 (1.8–6.3)	2.6 (1.4–5.0)	2.4 (1.2–4.3)
Gonadotropin	79	13 (16.5)	1.9 (1.1–3.5)	1.5 (0.8–2.8)	1.2 (0.6–2.3)
FSH/LH/GnRH	154	27 (17.5)	2.1 (1.4–3.3)	1.7 (1.1–2.6)	1.3 (0.8–2.1)
Other	37	6 (16.2)	1.9 (0.8–4.5)	1.5 (0.6–3.7)	1.2 (0.5–3.0)

RR: Relative risk. 95%CI: 95 percent confidence interval. IUI: Intrauterine insemination. ART: Assisted reproduction technologies (in vitro fertilization (IVF), intracytoplasmatic sperm injection (ICSI), and gamete intrafallopian transfer (GIFT)). FSH: Follicle stimulating hormone. LH: Luteinizing hormone. GnRH: Gonadotropin-releasing hormone.

[a] Adjusted for pre-pregnancy weight and parity.

[b] Adjusted also for multiple gestations

[c] Not mutually exclusive. Compared to women without fertility treatments.

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Table 4

Incidence of preeclampsia according to women's infertility history and accounting for multiple gestations.

		Preeclampsia			
	Total No.	**Incidence No. (%)**	**Model 1 Crude RR (95% CI)**	**Model 2[a] Adjusted RR (95% CI)**	**Model 3 [b] Adjusted RR (95% CI)**
Overall (N=5111)					
Fertility treatment					
No	4762	115 (2.4)	Reference	Reference	Reference
Yes	349	18 (5.2)	2.2 (1.3–3.7)	1.6 (1.0–2.7)	1.2 (0.7–2.2)
Singleton gestation (N=4947)					
Fertility treatment					
No	4680	110 (2.4)	Reference	Reference	NA
Yes	267	10 (3.8)	1.6 (0.8–3.1)	1.2 (0.6–2.4)	
Twins (N=142)					
Fertility treatment					
No	76	5 (6.6)	Reference	Reference	NA
Yes	66	5 (7.6)	1.2 (0.3–4.2)	0.6 (0.1–2.5)	

RR: Relative risk. 95%CI: 95 percent confidence interval.

[a] Adjusted for pre-pregnancy BMI and parity.

[b] Adjusted also for number of fetuses

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