Infertility, Fertility Treatment, and Risk of Hypertension

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Abstract

Objective—To evaluate the association between infertility and fertility treatments on subsequent risk of hypertension.

Design—Cohort Study

Setting—Nurses' Health Study II

Patients—116,430 female nurses followed from 1993 to June 2011 as part of the Nurses' Health Study II cohort.

Intervention—None

Main Outcome Measures—Self-reported, physician diagnosed hypertension

Results—Compared to women who never reported infertility, infertile women were at no greater risk of hypertension (multi-variable adjusted relative risk (RR) = 1.01 95% confidence interval [0.94–1.07]). Infertility due to tubal disease was associated with a higher risk of hypertension (RR=1.15 [1.01–1.31]) but all other diagnoses were not associated with hypertension risk

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compared to women who did not report infertility (ovulatory disorder: RR=1.03 [0.94–1.13], cervical: RR=0.88 [0.70–1.10], male factor: RR= 1.05 [0.95–1.15], other reason: RR=1.02 [0.94–1.11], reason not found: RR=1.02 [0.95–1.10]). Among infertile women there were 5,070 cases of hypertension. No clear pattern between use of fertility treatment and hypertension was found among infertile women (Clomiphene: RR =0.97 [0.90–1.04], Gonadotropin alone: RR=0.97 [0.87–1.08], IUI: RR=0.86 [0.71–1.03], IVF: RR=0.86 [0.73–1.01]).

Conclusion—Among this relatively young cohort of women, there was no apparent increase in hypertension risk among infertile women or among women who underwent fertility treatment in the past.

Keywords

Assisted Reproduction; Epidemiology; Infertility; IUI; IVF/ICSI Outcome

Introduction

In 2011 alone, over 151,000 In-Vitro Fertilization (IVF) cycles were performed in the United States to treat infertility.(1) However many other fertility treatments are utilized, including intrauterine insemination (IUI) with gonadotropins, gonadotropin injections alone, and clomiphene to help induce ovulation. Each of these treatments results in varying, elevated levels of endogenous hormones.

To our knowledge, no studies have examined the relation between infertility, fertility treatment, and development of hypertension. However, endogenous estrogen is postulated to decreases hypertension risk.(2) Thus, women who experience certain types of infertility, such as ovulatory disorder infertility, may experience altered hormonal levels which may alter risk. Additionally, current oral contraceptive use, which also alters the hormonal milieu, is associated with temporary increased blood pressure, as well as a potentially elevated risk of developing vascular disease later in life.(3–5) While fertility treatment may occur over a shorter duration of time than oral contraceptive use, the exogenous hormone exposure levels are much greater. In studies of potential mechanisms by which exogenous hormones may elevate blood pressure, the renin-angiotensin system has been implicated; current users of high-dose OCs have greatly elevated levels of angiotensinogen,(6) as well as of renin substrate concentration, and abnormalities of both renin activation and re-activation.(3) In a very small study of 8 infertility patients, ovarian stimulation was associated with marked stimulation of the renin-angiotensin-aldosterone system.(7) Even modest increases in blood pressure have significant implications for vascular health,(8) thus it is important to investigate how treatments for infertility patients may be related to long-term blood pressure levels. The Centers for Disease Control and Prevention have released a national public health action plan that outlines complications due to fertility treatment as an area of national research importance.(9)

Thus, we evaluated the association between fertility diagnosis, fertility treatment, and hypertension risk among participants in the Nurses' Health Study II. We believe that both the underlying infertility and fertility treatment had the potential to alter one's hypertension risk and thus it is important to quantify both factors.

Materials and Methods

The Nurses' Health Study II is a prospective cohort study, which began in 1989 when 116,430 registered nurses, 25–42 years old, returned a mailed questionnaire regarding their health and lifestyle. At recruitment, women lived in one of fourteen states, however the participants have since moved to all 50 states. Follow-up questionnaires are sent biennially. The follow-up rate from the original cohort is 92%. The study is approved by the Institutional Review Board of Brigham and Women's Hospital. Follow-up for the current analysis began in 1993 when women were first asked about fertility treatment and continues through 2009 questionnaires, which covers the time period from 1993 to May 2011 (when the 2009 questionnaire cycle ended).

Study population

Of the 116,430 women in the Nurses' health study we restricted our primary analysis of infertility to women who reported a specific type of infertility and non-infertile women. Since women who seek a medical evaluation for infertility differ from those women who do not on important demographic, lifestyle, and access factors (Farland, under review for publication) (10–18) additional analyses of infertility type were conducted using male factor infertility as the reference group. For these analyses, non-infertile women, women who reported infertility and never had a type identified, and women who reported other types of infertility were excluded. We restricted our analysis of fertility treatment to women who reported incident infertility or use of fertility treatment between 1993 and 2009 and who had been eligible to answer the most detailed question on fertility treatment on the 2009 questionnaires. In 2009, we stopped updating infertility and infertility treatment status because the majority of the cohort was well past reproductive age.

Assessment of infertility and treatment

To define infertility, women were asked if they had "tried to become pregnant for more than one year without success." Women were then asked what the cause for their infertility was and provided the following choices: tubal blockage, ovulatory disorder, endometriosis, cervical mucus factors, male factor infertility, not investigated, not found, and/or other. Women could report multiple causes for infertility. For the purpose of this analysis, we considered women who reported a cause for their infertility, excluding those who marked not investigated, as having had a medical evaluation for infertility.

On biennial questionnaires, women were asked if they had ever taken clomiphene or gonadotropin to induce ovulation. They were then prompted to report the number of months of clomiphene and gonadotropin use. In addition, on the 2009 questionnaire to collect further details, women were asked "have you ever used gonadotropins to treat infertility?"; those who answered yes were then asked to report how many cycles were utilized of: a) Gonadotropin injections alone: b) IUI, with Gonadotropin injections to stimulate ovulation; and c) IVF, with Gonadotropin injections to stimulate ovulation. All reports of fertility treatments were combined. In one set of analyses, we considered participants most advanced level of fertility treatment reported. Women were categorized by "strongest" treatment ever used, at a given follow-up period, into five potential categories: no treatment, clomiphene,

gonadotropin alone, IUI, and IVF. For example, if a woman reported clomiphene and IUI in 1995 this individual would be considered in the IUI category starting in 1995; in subsequent follow-up, her treatment category would be updated if she reported a "stronger" treatment, or carried forward if she reported no additional treatments. The second set of analyses addressed comprehensive treatment history. Women were categorized into one of eight categories based on all treatments reported: no treatment; clomiphene only; gonadotropin/IUI only; clomiphene + gonadotropin/IUI; clomiphene + IVF; gonadotropin/IUI + IVF; clomiphene + gonadotropin/IUI + IVF; IVF only. Referencing the same example, if a woman reported clomiphene and IUI in 1995, this individual would be categorized as clomiphene + gonadotropin/IUI beginning in 1995; her treatment category would then either be updated in subsequent follow-up if she initiated a new treatment, or carried forward through subsequent follow-up if no new treatments were reported.

Reliability and Validity of Self-Reported Fertility Treatment

While we believe that it is likely that these nurses would accurately report their use of fertility treatments, we evaluated the reliability and validity of self-reported fertility treatment. First, we compared gonadotropin use reported on each of the regularly mailed questionnaires from 1993–2009 with the single item in 2009 regarding lifetime history of gonadotropin use; we found very high reliability of reporting (concordance 84%) for the prospective reports versus the lifetime history question. In a validation study, we obtained medical records regarding fertility from 44 participants (with their signed permission); all of the records which provided information on fertility treatment (74% of the records) confirmed women's reported treatment, while the remaining records generally contained no information on specific treatments and thus were difficult to interpret.(19)

A prior validation of self-reported ovulatory disorder infertility was conducted among a random subset of 100 women in the Nurses' Health Study II who cited ovulatory disorder infertility as a potential reason for their infertility. In a supplemental questionnaire mailing to these women, 93% of women who responded reported diagnostic test results and/or indicative treatment for ovulatory disorder infertility. Additionally, 40 participant's medical records were reviewed, with 95% confirmation by diagnostic test and/or treatment.(20)

Assessment of hypertension

On each biennial questionnaire, women were asked if they had had physician diagnosed high blood pressure. The diagnosis date of hypertension was then set to the middle of the questionnaire cycle during which incident hypertension was reported. Of 85 women we sampled from NHS who had reported high blood pressure and responded to a validation questionnaire, only one denied elevated blood pressure (reporting that she in fact had hypotension).(21) Self reported hypertension was found to have high vaildity compared to the medical records. Of 51 women who reported hypertension for whom we were able to obtain medical records, hypertension (blood pressure greater than 140/90) was confirmed in all cases.(21)

Covariate Assessment

Many high blood pressure risk factors and risk factors for fertility treatment and infertility were considered a priori confounders and included in the multivariable models. Time-varying characteristics were derived from the most recent questionnaire in each two-year follow-up cycle. Status of the women's state mandated insurance coverage was based on reported state of residence at time of first reported infertility and categorized into no coverage and coverage. Household income before tax was reported in 2001. Menstrual cycle length and doctor diagnosed hirsutism were reported in 1993 and 1991 respectively. Other covariates of interest included age, body mass index (BMI), race, smoking history, parity, Alternative Healthy Eating Index (22), BMI at age 18, alcohol intake, physical activity, oral contraceptive use history, analgesic use, and total months of breast feeding. Time-varying covariates of interest were updated biennially.

Data Analysis

We used Cox proportional hazard models to evaluate the hazard ratio of incident high blood pressure. For analyses of infertility and infertility type, women who had never reported infertility were the reference group. Additional analyses of infertility type were conducted using male factor infertility as the reference group. For analyses of fertility treatments, infertile women who had never reported fertility treatment were the reference group with sensitivity analyses using non-infertile women as the reference group.

We constructed several models. Model 1 adjusted for age (continuous) and calendar time (continuous). Model 2 additionally adjusted for a priori confounders: BMI (kg/m^2) (<18.5, 18–22.5, 22.5–25, 25–30, >30), race (white, non-white), smoking (current, former, never), income (<$75,000, $ 75–99,999, $100,000–149,999, >$150,000), parity (nulliparous, 1, 2, 3, 4+ pregnancies), Alternative Healthy Eating Index (quintiles), BMI at 18 (<18.5, 18–22.5, 22.5–25, 25–30, >30), state mandated insurance coverage for fertility treatment (Yes/No), alcohol intake (no alcohol, >0–5 grams per day, 5.01–10 g per day, > 10 g per day), physical activity (METs/week) (<3, 3–<9, 9–<18, 18–<27, 27–<42, 42), oral contraceptive use (never, past, current), analgesic use (2+times/week)(yes/no), total months of breast feeding (never, <1 month, 1–3 months, 4–6 months, 7–12 months, 13–24 months, 25–36 months, > 36 months). In addition, in analyses with infertility as the exposure, we additionally adjusted model 2 for type of infertility: ovulatory disorder infertility (yes/no), tubal infertility (yes/no), cervical/mucosal factor (yes/no), male factor (yes/no), other reason (yes/no), not found (yes/no), not investigated (yes/no); and for treatment (no treatment, clomiphene, gonadotropin alone, IUI, IVF).

In a third model, we further adjusted for menstrual cycle length (<31 days, 32–39 days, greater than 40 days), physician diagnosed hirsutism (yes/no). In analyses of fertility treatment, model 3 additionally adjusted for ovulatory disorder infertility (yes/ no) and tubal infertility (yes/no).

Since tubal infertility has several specific risk factors, we conducted analyses of tubal infertility adjusting for additional potential confounding variables. We also adjusted for history of sexual abuse.(23) We also more finely adjusted for race/ethnicity (white (ref),

Hispanic, black, other) and household income (<$15,000, $15–19,999, $20–29,999, $30–39,999, $40–49,999, $50–74,999, $75–99,999, $100– 149,999, $150,000). We also adjusted for endometriosis, since findings from our research group indicate that endometriosis may increase risk of hypertension (Mu, submitted for publication).

Results

In 2001, approximately midway through our study, participants were 37 to 54 years old (Table 1). Women who used IVF were younger (mean= 43.8 (SD=4.0) years vs. 46.6 years (4.5)), had lower BMI (24.7 (5.1) vs. 25.9 (5.6)), more likely to be nulliparous (46% vs. 20%), more likely to have household income >$150,000 (25% vs. 12%), and more likely to live in states with mandated insurance coverage (22% vs. 15%) than their infertile counterparts who did not utilize fertility treatment. After over twenty years of follow-up, approximately 20,066 women were diagnosed with hypertension. 29,435 women reported having failed to become pregnant and 12,183 reported having used fertility treatment.

After adjustment for potential confounders, infertile women overall and women with specific infertility diagnoses were not at higher risk for hypertension (Table 2). Compared to women who did not report infertility, women reporting having ever experienced infertility were not at higher risk of hypertension during follow-up (relative risk [RR]=1.01 95% confidence interval [CI]:0.94–1.07). Compared to women who did not report infertility, women with most infertility diagnoses did not appear to have an increased risk for hypertension after adjustment for confounding factors (ovulatory disorder: RR=1.03 CI: 0.94–1.13, cervical mucus: RR=0.88 CI:0.70–1.10, male factor: RR= 1.05 CI:0.95–1.15, other reason: RR=1.02 CI:0.94–1.11, reason not found: RR=1.02 CI:0.95–1.10). The attenuation of apparent risk for hypertension in ovulatory disorder infertility from model 1 to the final model was driven primarily by adjustment for BMI. Women with tubal infertility appeared at slight increased risk for hypertension (RR=1.15 CI:1.01–1.31). In sensitivity analyses, more fine adjustment for race/ethnicity, household income, and sexual abuse history did not attenuate this relation. When utilizing a comparison group of women reporting male factor infertility, there was no increased risk for any infertility type (ovulatory disorder: RR=1.11 CI:0.95–1.28, tubal: RR=1.07 CI:0.87–1.32, cervical mucus: RR=0.96 CI:0.76–1.22, other reason: RR=0.93 CI:0.80–1.07, reason not found: RR=0.88 CI:0.73–1.06).

Among infertile women, we examined the risk of hypertension among women who had fertility treatment, according to their most advanced type of treatment (Table 3). After adjustment for a priori confounding factors, there was no difference in risk for women who reported any fertility treatment utilization compared to women who had not used treatment (clomiphene: RR=0.97 CI:0.90–1.04; Gonadotropin alone: RR=0.97 CI:0.87–1.08, IUI: RR= 0.86 CI:0.71–1.03, IVF:RR= 0.86 CI:0.73–1.01). Results did not change meaningfully when those with infertility treatment were compared to women who did not report infertility (data not shown).

Among infertile women, we also examined the relative risk of high blood pressure according to comprehensive fertility treatment history (Table 4). Similarly, after adjustment for a priori

confounding factors, there was no significant difference in high blood pressure risk for women who reported fertility treatment compared to those who had not used treatment (clomiphene only: RR= 0.97 CI:0.90–1.04, gonadotropin alone/IUI alone: RR=1.02 CI: 0.83–1.24; clomiphene + gonadotropin/IUI: RR=0.93 CI:0.83–1.04; clomiphene+ IVF: RR=0.83 CI:0.66–1.05; gonadotropin/IUI + IVF: RR=0.84 CI:0.50–1.43; clomiphene + gonadotropin/IUI + IVF: RR=0.94 CI:0.72–1.23; IVF only: RR=0.82 CI:0.55–1.22). In sensitivity analyses conducted with women who did not report infertility as the comparison group, similarly there was no relation of comprehensive treatment history and risk for high blood pressure (data not shown).

Discussion

In this analysis of infertility, fertility treatment, and risk of hypertension we found that there was no increased risk of hypertension among women with infertility or among women who utilized infertility treatments. The sole exception was women with a diagnosis of infertility due to tubal disease who had a 15% greater risk of hypertension than women without a history of infertility. The present literature on fertility treatment and hypertension is limited. Often times in studies conducted within a fertility-clinic based population it is difficult to delineate the independent effect of the infertility diagnosis and the infertility treatment. A strength of this study is its ability to answer this question by comparing those who utilized fertility treatment to those with reported infertility who did not receive treatment.

When assessing the effect of underlying infertility on hypertension risk, we found no increased risk of hypertension for overall infertility or for most types of infertility. The exception in our analyses was the finding that women with tubal infertility were at increased risk for hypertension compared to non-infertile women. A leading cause of tubal infertility is undiagnosed and untreated sexually transmitted diseases. Thus there may differences in the distribution of socio-economic factors that alter ones hypertension risk which were not accounted for adequately in our analyses. Alternatively, tubal infertility could be an intermediate marker for STIs and inflammation which may increase risk of hypertension. In addition, we have previously found positive associations between infertility due to tubal disease and risk of other cardio-metabolic conditions including gestational diabetes (24) and type 2 diabetes (Tobias, under review for publication). However, we found no relation of tubal infertility to hypertension when using a comparison group of male factor infertility. Since couples who seek a medical evaluation for infertility vary on a variety of demographic, lifestyle, and access factors from their infertile counterparts with uninvestigated infertility, (19) (Farland, Under review for publication) it was important to compare the effect of type of infertility within women who had sought an evaluation for their fertility (using male factor infertility as the reference group). Our findings for the association between tubal infertility and hypertension differed depending on the group to whom the tubal infertility was compared. Tubal infertility was not associated with hypertension when compared to male factor infertility, however tubal infertility was significantly associated with hypertension when compared to women who never reported infertility. This difference by comparison group may be influenced by sample size, remaining unknown / unadjusted confounders, measurement error in specifying infertility

diagnoses, or simply that the male factor group represents women with a risk profile for hypertension dissimilar to those who did not seek treatment for their infertility.

Among infertile women, those women who sought treatment for their infertility were not found to be at an increased risk of hypertension compared to women who did not utilize treatment. This is despite short-term, altered levels of endogenous and exogenous hormones. Gonadotropin injections utilized alone and in combination with IUI and IVF raise endogenous levels of estrogen and progesterone, and in an IVF cycle, high doses of progesterone are administered for the two weeks subsequent to embryo transfer. Our analyses focused on longer-term rather than acute/temporary risk of hypertension, and thus our null findings may be consistent with the effect of oral contraceptive use being strongest among current OC users and attenuating after discontinuation.(4)

In addition to our inability to identify acute and temporary effects of fertility treatment on hypertension risk, there are other limitations to consider. All variables in our analyses were based on self-report, which may cause non-differential misclassification in a prospective study. However, we found high reliability and validity of self-reported fertility treatment compared to medical records (19) and of self-reported ovulatory disorder infertility compared to medical records.(20) Similarly, hypertension appeared virtually perfectly reported in our validation study. Thus, any bias to the null caused by non-differential misclassification of the outcome is likely to be very modest. The population under study was homogenous in terms of race and education level thus these results should be generalized with caution, especially to under-represented racial and ethnic groups who often have differential risks of hypertension compared to Caucasians. This study has several strengths including its large sample size, temporal evaluation of predictors and outcome, high follow-up rate, and information on both infertility and treatment. Of particular importance is the ability to compare and contrast women who are infertile and received treatment to those are infertile and did not utilize treatment.

In sum, women who are infertile or who have utilized fertility treatments do not appear to be at longer-term increased risk of hypertension.

Acknowledgments

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Table 1

Characteristics of women with infertility by treatment status: Nurses' Health Study II in 2001

	Most advanced treatment level reported				
	No treatment (n=8,261)	Clomiphene (n=4,367)	Gonadotropin (n=1,485)	IUI (n=508)	IVF (n=851)
Age (years) *	46.6 (4.5)	45.7 (4.6)	45.1 (4.2)	43.7 (4.2)	43.8 (4.0)
Alcohol intake (gm/week)	3.8 (7.0)	3.8 (6.8)	4.0 (6.6)	3.9 (6.7)	4.7 (7.8)
Alternative healthy eating index	52.8 (11.5)	52.4 (11.1)	53.9 (11.2)	53.4 (11.4)	55.8 (11.1)
Body Mass Index (BMI) (kg/m2)	25.9 (5.6)	26.0 (5.6)	25.6 (5.5)	26.0 (5.5)	24.7 (5.1)
White race, %	94	95	95	96	95
Family history of hypertension, %	50	51	51	51	46
History of pregnancies > 6 months					
- Nulliparous, %	20	19	31	37	46
- 1 pregnancy, %	19	20	30	28	28
- 2 pregnancies, %	38	37	27	24	21
- 3 pregnancies, %	17	18	9	8	4
- 4+ pregnancies, %	7	6	3	3	1
Current oral contraceptive use					
- Never, %	12	10	11	13	14
- Past, %	81	82	82	78	80
- Current, %	7	8	7	9	6
Menstrual cycle length (days)					
- <31, %	85	75	78	81	86
- 32–39, %	9	15	12	11	10
- >40, %	5	10	10	8	4
Physician diagnosed hirsutism, %	3	5	5	2	3
Analgesic use (2+ times/week), %	46	45	44	41	43
Smoking history					
- Never, %	65	67	65	68	64
- Past, %	25	26	28	24	29
- Current, %	9	7	8	8	7
Household income (dollars/year)					

	Most advanced treatment level reported				
	No treatment (n=8,261)	Clomiphene (n=4,367)	Gonadotropin (n=1,485)	IUI (n=508)	IVF (n=851)
- <75,000, %	44	39	34	35	29
- 75,000–99,999, %	22	22	21	21	20
- 100,000–150,000, %	22	24	25	25	25
- >150,000, %	12	14	19	20	25
Live in state with mandated insurance coverage					
- No coverage, %	85	89	82	83	78
- Comprehensive coverage, %	1	1	2	1	2
- Limited coverage, %	6	4	7	7	9
- Offer only, %	8	6	9	9	11
**Fertility diagnosis among those who had a medical evaluation					
Ovulatory disorder infertility reported, %	11	53	52	51	34
Tubal infertility reported, %	8	10	15	12	31
Cervical mucus infertility reported, %	3	8	14	16	13
Male factor infertility reported, %	16	19	26	35	29
Other reason for infertility reported, %	22	33	45	47	57

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding

*
Value is not age adjusted

**
Categories not mutually exclusive

Table 2

The relative risk of hypertension by fertility status: Nurses' Health Study II

	Hypertension Cases; person-years	Model 1	Model 2 Relative Risk (95% CI)	Model 3
Never-infertile women	14,761;757,404	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Infertile women	5,305; 253,964	1.04 (1.01, 1.07)	1.01 (0.95, 1.08)	1.01 (0.94, 1.07)
		Infertility Diagnoses[*]		
Never-infertile women	14,761;757,404	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Ovulatory disorder infertility	1,659; 74,254	1.18 (1.12, 1.24)	1.05 (0.96, 1.15)	1.03 (0.94, 1.13)
Tubal infertility	627; 27,194	1.14 (1.05, 1.23)	1.15 (1.01, 1.31)	1.15 (1.01, 1.31)
Cervical mucus factor	292; 15,727	0.96 (0.85, 1.07)	0.88 (0.70, 1.10)	0.88 (0.70, 1.10)
Male factor infertility	1,017; 49,808	1.04 (0.97, 1.11)	1.04 (0.94, 1.15)	1.05 (0.95, 1.15)
Other reason	1,487; 73,683	1.01 (0.96, 1.07)	1.02 (0.94, 1.11)	1.02 (0.94, 1.11)
Reason for infertility not found	1,262; 63,926	0.99 (0.93, 1.05)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
		Among Women with Infertility Evaluation[*]		
Male factor infertility	1,017; 49,808	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Ovulatory disorder infertility	1,659; 74,254	1.21 (1.10, 1.32)	1.12 (0.97, 1.30)	1.11 (0.95, 1.28)
Tubal infertility	627; 27,194	1.11 (1.00, 1.24)	1.07 (0.87,1.31)	1.07 (0.87, 1.32)
Cervical mucus factor	292; 15,727	0.92 (0.80, 1.06)	0.96 (0.75, 1.21)	0.96 (0.76, 1.22)
Other reason	1,487; 73,683	0.95 (0.87, 1.05)	0.92 (0.80, 1.07)	0.93 (0.80, 1.07)
Reason for infertility not found	1,262; 63,926	0.93 (0.85, 1.02)	0.88 (0.73, 1.07)	0.88 (0.73, 1.06)

Model 1: Age and calendar time adjusted

Model 2: Model 1 + BMI (kg/m^2) (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), Race (White(ref), non-white), smoking (current, former, never(ref)), income (<$75,000, $ 75–99,999, $100,000–149,999, >$150,000), parity (nulliparous (ref), 1, 2, 3, 4+ pregnancies), Alternative healthy eating index (quintiles), BMI at 18 (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), family history of hypertension (yes/no), state mandated insurance coverage for fertility treatment (Yes/No), alcohol intake (drinks no alcohol per day (ref), drinks >0–5 gm alcohol per day, drinks 5.01–10 gm alcohol per day, drinks > 10 gm alcohol per day), Physical Activity (METs/week) (<3 (Ref), 3–<9, 9–<18, 18–<27, 27–<42, 42), Oral contraceptive use (Never (Ref), Past, Current), analgesic use (2+times/week)(yes/no), total breast feeding (Never, <1 month, 1–3 months, 3–6 months, 6–12 months, 12–24 months, 24–36 months, > 36 months), Ovulatory Infertility (yes/no), Tubal infertility (yes/no), Cervical/mucosal factor (yes/no), Male factor (yes/no), other reason (yes/no), not found (yes/no), not investigated (yes/no), treatment group (No treatment(ref), Clomiphene alone, Gonadotropin alone, IUI,IVF),

Model 3: Model 2 + menstrual cycle length (<31 days (ref), 32–39 days, greater than 40 days), physician diagnosed hirsutism (yes/no)

[*] Categories are not mutually exclusive

Table 3

Among infertile women, the relative risk of hypertension by most advanced level of fertility treatment: Nurses' Health Study II

Treatment	Hypertension Cases; Person-years	Model 1	Model 2 Relative Risk (95% CI)	Model 3
No Treatment	2,844; 131,052	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Clomiphene alone	1,482; 71,584	1.03 (0.96, 1.09)	1.01 (0.95, 1.08)	0.97 (0.90, 1.04)
Gonadotropin alone	444; 23,008	0.97 (0.87, 1.07)	1.02 (0.92, 1.14)	0.97 (0.87, 1.08)
IUI	123; 7,427	0.89 (0.74, 1.07)	0.89 (0.74, 1.07)	0.86 (0.71, 1.03)
IVF	177; 12,208	0.75 (0.64, 0.88)	0.91 (0.78, 1.07)	0.86 (0.73, 1.01)

Model 1: Age and calendar time adjusted

Model 2: Model 1 + BMI (kg/m^2) (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), Race (White(ref), non-white), smoking (current, former, never(ref)), income (<$75,000, $ 75–99,999, $100,000–149,999, >$150,000), parity (nulliparous (ref), 1, 2, 3, 4+ pregnancies), Alternative healthy eating index (quintiles), BMI at 18 (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), family history of hypertension (yes/no), state mandated insurance coverage for fertility treatment (Yes/No), alcohol intake (drinks no alcohol per day (ref), drinks >0–5 gm alcohol per day, drinks 5.01–10 gm alcohol per day, drinks > 10 gm alcohol per day), Physical Activity (METs/week) (<3 (Ref), 3–<9, 9–<18, 18–<27, 27–<42, 42), Oral contraceptive use (Never (Ref), Past, Current), analgesic use (2+times/week)(yes/no), total breast feeding (Never, <1 month, 1–3 months, 3–6 months, 6–12 months, 12–24 months, 24–36 months, > 36 months)

Model 3: Model 2 + Ovulatory Infertility (yes/ no), Tubal Infertility (yes/no), menstrual cycle length (<31 days (ref), 32–39 days, greater than 40 days), physician diagnosed hirsutism (yes/no)

Table 4

Among infertile women, the relative risk of hypertension by comprehensive fertility treatment history: Nurses' Health Study II

Treatment	Hypertension Cases; Person-years	Model 1	Model 2 Relative Risk (95% CI)	Model 3
No Treatment	2,844; 132,052	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Clomiphene	1,482; 71,584	1.03 (0.96, 1.09)	1.01 (0.95, 1.08)	0.97 (0.90, 1.04)
Gonadotropin alone/IUI	106; 5,347	0.96 (0.79, 1.17)	1.05 (0.86, 1.29)	1.02 (0.83, 1.24)
Clomiphene + Gonadotropin/IUI	461; 25,088	0.94 (0.85, 1.04)	0.98 (0.88, 1.09)	0.93 (0.83, 1.04)
Clomiphene + IVF	78; 5,024	0.76 (0.61, 0.96)	0.88 (0.70, 1.11)	0.83 (0.66, 1.05)
Gonadotropin/IUI + IVF	14; 1,099	0.66 (0.39, 1.12)	0.88 (0.51, 1.49)	0.84 (0.50, 1.43)
Clomiphene + Gonadotropin/IUI + IVF	60, 4,060	0.82 (0.63, 1.06)	0.99 (0.76, 1.29)	0.94 (0.72, 1.23)
IVF	25; 2,025	0.64 (0.43, 0.96)	0.87 (0.58, 1.30)	0.82 (0.55, 1.22)

Model 1: Age and calendar time adjusted

Model 2: Model 1 + BMI (kg/m^2) (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), Race (White(ref), non-white), smoking (current, former, never(ref)), income (<$75,000, $75–99,999, $100,000–149,999, >$150,000), parity (nulliparous (ref), 1, 2, 3, 4+ pregnancies), Alternative healthy eating index (quintiles), BMI at 18 (<18.5, 18–22.5 (ref), 22.5–25, 25–30, >30), family history of hypertension (yes/no), state mandated insurance coverage for fertility treatment (Yes/No), alcohol intake (drinks no alcohol per day (ref), drinks >0–5 gm alcohol per day, drinks 5.01–10 gm alcohol per day, drinks > 10 gm alcohol per day), Physical Activity (METs/week) (<3 (Ref), 3–<9, 9–<18, 18–<27, 27–<42, 42), Oral contraceptive use (Never (Ref), Past, Current), analgesic use (2+times/week)(yes/no), total breast feeding (Never, <1 month, 1–3 months, 3–6 months, 6–12 months, 12–24 months, 24–36 months, > 36 months)
Model 3: Model 2 + Ovulatory Infertility (yes/ no), Tubal Infertility (yes/no), menstrual cycle length (<31 days (ref), 32–39 days, greater than 40 days), physician diagnosed hirsutism (yes/no)