

Infertility, fertility treatment, and risk of hypertension

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

Design: Cohort study.

Setting: Not applicable.

Patient(s): A total of 116,430 female nurses, followed from 1993 to June 2011, as part of the Nurses' Health Study II cohort.

Intervention(s): None.

Main Outcome Measure(s): Self-reported, physician-diagnosed hypertension.

Result(s): Compared with women who have never reported infertility, infertile women were at no greater risk of hypertension (multivariable adjusted relative risk (RR) = 1.01, with 95% confidence interval [CI] [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 no other diagnoses were associated with hypertension risk, compared with 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]). Infertile women collectively had 5,070 cases of hypertension. No clear pattern between use of fertility treatment and hypertension was found among infertile women (clomiphene citrate: RR = 0.97 [0.90–1.04]; gonadotropin alone: RR = 0.97 [0.87–1.08]; intrauterine insemination: RR = 0.86 [0.71–1.03]; in vitro fertilization: RR = 0.86 [0.73–1.01]).

Conclusion(s): Among this relatively young cohort of women, no apparent increase occurred in hypertension risk among infertile women, or among women who had undergone fertility treatment previously. (Fertil Steril® 2015;104:391–7. ©2015 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction, epidemiology, infertility, IUI, IVF/ICSI outcome

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In 2011 alone, more than 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 citrate

(CC) to help induce ovulation. Each of these treatments results in varying, elevated levels of endogenous hormones.

To our knowledge, no studies have examined the relationship among infertility, fertility treatment, and development of hypertension. However, endogenous estrogen is postulated to

decrease 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. Current oral contraceptive (OC) use, which alters the hormonal milieu, is associated with temporarily increased blood pressure, as well as a potentially elevated risk of developing vascular disease later in life (3–5). Although fertility treatment may occur over a shorter duration of time than OC 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

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elevated levels of angiotensinogen (6) and renin substrate concentration, as well as abnormalities of both renin activation and reactivation (3).

In a 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, an important avenue of investigation is the relationships, if any, of fertility treatments with long-term blood pressure levels. The Centers for Disease Control and Prevention released a national public health action plan that outlines complications that are due to fertility treatment as an area of national research importance (9).

We evaluated the associations of fertility diagnosis and fertility treatment with hypertension risk among participants in the Nurses' Health Study II. We believe that both the underlying infertility, and the fertility treatment, have the potential to alter hypertension risk; thus, quantification of both is important.

MATERIALS AND METHODS

The Nurses' Health Study II is a prospective cohort study, which began in 1989, when 116,430 registered nurses, aged 25 to 42 years, returned a mailed questionnaire regarding their health and lifestyle. At recruitment, women lived in 1 of 14 states; however, participants have since moved, and now collectively live in 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 the 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 II, we restricted our primary analysis of infertility to women who either reported a specific type of infertility or were noninfertile women. Given that women who seek a medical evaluation for infertility differ from those who do not, on important demographic, lifestyle, and access factors (Farland, personal communication, September 2014) (10–18), additional analyses of infertility type were conducted using male factor infertility as the reference group. For these additional analyses, non-infertile women, women who reported infertility and never had a type identified, and women who reported types of infertility other than the type under analysis 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 since this question contributed to our exposure definition. In 2009, we stopped updating infertility and fertility treatment status because most 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 who responded "Yes" were considered infertile. Women were asked what the cause of their infertility was, and given 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 of 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 CC or gonadotropin to induce ovulation, and if so, for how many months. In addition, on the 2009 questionnaire, women were asked if they had ever used gonadotropins to treat infertility, and if so, how many cycles. They were asked to indicate if the treatment was: (1) gonadotropin injections alone; (2) IUI, with gonadotropin injections to stimulate ovulation; or (3) IVF, with gonadotropin injections to stimulate ovulation. Reports of fertility treatments from the biennial questionnaires and collected in 2009 were combined.

In one set of analyses, we considered participants' most advanced level of fertility treatment reported. Women were categorized by the "most advanced" treatment ever used, at a given follow-up period, into 5 potential categories: no treatment, CC, gonadotropin alone, IUI, and IVF. For example, if a woman reported CC and IUI in 1995, she would be considered to be in the IUI category starting in 1995; in subsequent follow-up, her treatment category would be updated if she reported a "more advanced" treatment, or carried forward if she reported no additional treatments.

The second set of analyses addressed comprehensive treatment history. Women were categorized into 1 of 8 categories based on all treatments reported: no treatment; CC only; gonadotropin/IUI only; CC + gonadotropin/IUI; CC + IVF; gonadotropin/IUI + IVF; CC + gonadotropin/IUI + IVF; IVF only. Referencing the same example, if a woman reported CC and IUI in 1995, she would be categorized as CC + gonadotropin/IUI beginning in 1995; her treatment category would 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

Although 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 to 2009 with the single item in 2009 regarding lifetime history of gonadotropin use; we found very high reliability of reporting (concordance $\geq 84\%$) for the prospective reports vs. the lifetime history question. In a validation study, we obtained medical records regarding fertility from 44 participants (with their signed permission); all the records that provided information on fertility treatment (74% of the records) confirmed women's reported treatment, whereas the remaining records generally contained no information on specific treatments and thus were difficult to interpret (19).

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