

Use of fertility treatment modalities in a large United States cohort of professional women

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Objective: To evaluate the use of fertility treatments among a large cohort of women in the United States.

Design: Cohort study.

Setting: Nurses' Health Study II.

Patient(s): Ten thousand thirty-six women who reported having used fertility treatment on biennial questionnaires from 1993–2009.

Intervention(s): None.

Main Outcome Measure(s): Data on patterns of treatment modality were collected via self-report from validated mailed questionnaires. Information on clomiphene, gonadotropin injections alone, and gonadotropin injections as part of intrauterine insemination (IUI) and in vitro fertilization (IVF) was queried.

Result(s): Most women who reported fertility treatment used clomiphene (94%), with a large majority reporting clomiphene as their only form of treatment (73%). Of women who reported treatment more advanced than clomiphene, 13% had used gonadotropin injections alone, 11% IUI treatment, and 11% IVF. Several subgroups were more likely to use multiple treatment modalities and to initiate treatment with gonadotropins rather than clomiphene, including women living in states with insurance coverage of fertility procedures, with higher household income, younger in age, who remained nulliparous at the study close, and treated after 2000.

Conclusion(s): Results should be interpreted cautiously, but to our knowledge, this represents the first study of fertility treatment patterns in the United States and could inform public health planning. (Fertil Steril® 2014; ■:■–■. ©2014 by American Society for Reproductive Medicine.)

Key Words: Fertility treatment, IVF, IUI, clomiphene, gonadotropins

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Infertility influences millions of couples each year (1), with recent national estimates of infertility ranging from 6.0% (2) to 15.5% (3). In 2010, over 147,000 in vitro fertilization (IVF) procedures to treat infertility were administered in the United States (4). While the number of women using IVF treatment has steadily risen over

the past three decades (4), there is no clear understanding of the prevalence and patterns of different fertility treatment modalities among women using fertility treatments since there are no established registries for tracking such information.

Using the Nurses' Health Study II cohort, we evaluated patterns of fertility

treatment modalities for the purposes of informing public health planning, estimating some of the costs associated with infertility, and evaluating the long-term health outcomes. The Nurses' Health Study II is a unique data source with information on a variety of prescription fertility treatments reported by participants on regular questionnaires from 1993 through 2009. The population using infertility treatments in the United States tends to be of high socioeconomic and educational status (5), and thus, our population of health professionals may fairly well represent the use of fertility treatments by the general population of fertility patients.

We present data from 10,036 women who reported use of fertility

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treatment from 1993 to 2009. We hypothesize that financial factors, such as household income and state-mandated insurance coverage, as well as biologic or temporal patterns such as parity, age, and decade of treatment, will influence treatment use patterns, and thus we conducted stratified analyses by these variables.

METHODS

Study Population

The Nurses' Health Study II is a prospective cohort study that began in 1989, when 116,430 registered nurses aged 25–42 years returned a mailed questionnaire regarding their health and lifestyle. At recruitment, women lived in one of 14 states: California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas; 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.

The current analysis is an investigation of patterns in the reported use of fertility treatment in the Nurses' Health Study II. Follow-up for the current analysis began in June 1993, when participants were first asked about treatments for infertility; data are included from the 1993–2009 questionnaires, which cover the time period from June 1993 to May 2011 (when the 2009 questionnaire cycle ended).

Collection of Information on Fertility Treatment

For the purpose of this manuscript, we defined fertility treatment as clomiphene and gonadotropin injections (either with or without intrauterine insemination (IUI) and IVF/ART). Women were asked whether they had taken “clomiphene or gonadotropins (yes/no) to induce ovulation” over the previous 2 years on six questionnaires in 1993, 1995, 1997, 2001, 2005, and 2009. Women who marked “yes” were then asked to separately provide the number of months of clomiphene and of gonadotropin usage since the previous mailed questionnaire. Additionally, in 2009, women were asked a more detailed question specifically regarding their lifetime history of gonadotropin injections to treat infertility, including specific information on the type of treatment in which gonadotropins had been used (i.e., gonadotropin injection alone, gonadotropins for IUI, gonadotropins for IVF). With these data, we categorized women's use of each of four treatments, which was defined as a report at any time from 1993 through 2011 of clomiphene, gonadotropin injections alone, gonadotropin injections with IUI, or gonadotropin injections with IVF.

Reliability and Validity of Self-reported Fertility Treatment

Although we thought it was unlikely that women would not accurately report their use of fertility treatments, since it is usually a major event in a woman's life, we evaluated the reliability and validity of self-reported fertility treatment. We compared the gonadotropin use reported on each of the

regularly mailed questionnaires from 1993–2009 with the single item in 2009 regarding a lifetime history of gonadotropin use; we found very high reliability of reporting (concordance $\geq 84\%$) 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 that mentioned fertility treatment (74% of the records) confirmed women's reported treatment, while the remaining records generally contained no information on specific treatments.

Data Analysis

We evaluated the distribution of characteristics of women in our cohort at the time of first report of fertility treatment using data from the biennial questionnaires. These characteristics included body mass index (BMI), cigarette smoking status (categorized as current, former, and never smoking), and race/ethnicity (categorized as white, black, American Indian, Asian, Hawaiian, multiracial, other).

We considered several biological, economic, and other factors that might modify treatment patterns, including parity in 2009 (as a proxy for severity of underlying infertility), infertility insurance coverage, household income, decade of initial treatment, and age at first reported fertility treatment. Specifically, information on pregnancies was collected on each biennial questionnaire; thus, updated information was available on parity, which was categorized in 2009 as nulliparous or parous. In 2001, women were asked about pretax annual household income. We created five categories: $< \$50,000$, $\$50,000$ – $75,000$, $\$75,000$ – $\$99,999$, $\$100,000$ – $150,000$, and $> \$150,000$. For assessing insurance coverage of fertility treatment, we used our data on women's state of residence at the time that they reported initial fertility treatment; women were considered to be from an uninsured state if their state did not have mandated coverage of fertility treatment of any kind during the year in which they first reported fertility treatment during the 1993–2009 follow-up period. For assessing age at fertility treatment, we used data on women's age when they reported their first fertility treatment. Women were then categorized by age according to the Society of Assisted Reproductive Technologies' guidelines of < 35 years, 35–37 years, 38–40 years, and > 40 years old. For assessing time the period of fertility treatment, we used the date when they first reported fertility treatment. Women were categorized as having had treatment during the 1990s or after 2000; 2000 represented the approximate midpoint of our study follow-up. In analyses comparing fertility treatment use across categories, we used a χ^2 -test to assess statistical differences between groups.

RESULTS

In our population of women reporting fertility treatment at anytime during follow-up ($n = 10,036$; Table 1), the mean age at the time of the first reported fertility treatment was 37.7 years (SD = 4.3). The mean BMI at the time of the first reported fertility treatment was 25.4 kg/m^2 (SD = 5.9), with 36.9% overweight or obese ($\geq 25.0 \text{ kg/m}^2$). At the initial time of reported treatment, 7.8% of women reported current

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