Oral Contraceptives and Ovulatory Causes of Delayed Fertility

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The return of fertility for women who discontinue oral contraceptives takes longer as compared with women who discontinue other methods of contraception. It remains unclear, however, whether subsequent fertility differs according to duration or age at first use. The authors performed a nested case-control study within a cohort of 116,686 female registered nurses residing in 14 US states. Baseline information was reported on mailed questionnaires in 1989. Cases comprised 1,917 married nurses without previous pregnancy who were unable to become pregnant for at least 1 year and were subsequently diagnosed with primary ovulatory infertility. Controls comprised 44,521 married parous nurses with no history of infertility and no pregnancies lasting less than 6 months. After allowing for 2 years of suppressed fertility following discontinuation of oral contraceptive use and excluding women with signs of menstrual or hormonal disorder, the authors found that the multivariate relative risk for ovulatory causes of delayed fertility was 1.2 (95% confidence interval 0.7–1.9) for ever users. There was no statistically significant trend of increasing risk with increasing duration of use and younger age at first use. The fact that 88 percent of cases reported an eventual pregnancy by 1993 suggests that absolute fertility was not impaired.


contraceptives, oral; infertility, female; ovulation

The return of fertility for women who discontinue oral contraceptives takes longer as compared with women who have used other methods of contraception (1–8). It remains uncertain, however, whether subsequent fertility differs according to duration of oral contraceptive use or age at first use. Although oral contraceptive use declined in American women from 1973 to 1982, use increased among the youngest age group (12–19 years) from the 1970s to the early 1980s (9). Because this group of early users will also tend to have a longer duration of use, it is important to determine whether this pattern of oral contraceptive use has an impact on subsequent fertility. We examined the association between duration of oral contraceptive use, age at first use, and impaired fertility due to ovulatory disorder using a case-control design nested within a cohort of 116,686 US female nurses.

MATERIALS AND METHODS

Study population

The Nurses’ Health Study II began in 1989 when 116,686 female registered nurses between the ages of 25 and 42 years and living in 14 states completed a mailed questionnaire that included items about their medical history, oral contraceptive use, parity, and menstrual patterns during adolescence. In 1991 and 1993, follow-up questionnaires were mailed to update the information on oral contraceptive use and to identify newly diagnosed cases of a variety of medical conditions; the response rates were 93 percent and 92 percent, respectively.

Ascertainment of ovulatory causes of impaired fertility

On the baseline questionnaire, 18.3 percent (n = 21,378) of respondents answered affirmatively to the question, “Have you ever tried to become pregnant for more than one year without success?” These women were then asked, “What was the cause? (mark all that apply): tubal blockage, ovulatory disorder, endometriosis, cervical mucous factors, spouse, not investigated,
not found, other.” Of these women, 5,798 marked ovulatory disorder. For the present analysis, we defined cases as ever-married women who reported diagnosis of ovulatory infertility without endometriosis, tubal blockage, or spousal infertility; 3,605 women met this case definition. Because we were interested in primary infertility, we then further excluded women who had a pregnancy of any duration prior to diagnosis of ovulatory infertility (n = 1,500). Controls consisted of ever-married nurses who reported no infertility and who had a first pregnancy lasting greater than or equal to 6 months; 62,328 met the control definition. We then excluded controls with a history of a pregnancy lasting less than 6 months (n = 12,973) because a prior miscarriage could reflect an inability to carry to term and be associated with impaired fertility.

We assessed the validity of self-report of diagnosis of ovulatory infertility by sending supplementary questionnaires to 100 randomly selected participants who reported primary ovulatory infertility. The questionnaire sought details of the diagnosis and treatment for infertility and included a request for permission to review medical records. Ninety nurses responded to the supplementary questionnaire; of these, 89 percent reported a confirmatory diagnostic test (abnormal basal body temperature charts, progesterone assay, endometrial biopsy, or other confirmatory test), 82 percent reported confirmatory treatment (Clomid (Marion Merrell Dow, Inc., Kansas City, Missouri); Pergonal (Serono Laboratories, Inc., Norwell, Massachusetts), human chorionic gonadotropin, or other confirmatory treatment), 93 percent reported either confirmatory diagnosis or treatment, and 78 percent reported both. Seventy-one women gave permission to review their medical records; however, because of the long duration since infertility evaluations for many participants, many clinic records had been destroyed and could not be obtained. Of the 40 medical records we located, 95 percent confirmed the diagnosis by either a diagnostic test or specific treatment for ovulatory infertility. Hence, in this analysis, we relied upon the nurses’ self-report of their diagnosis.

Conception after infertility classification is consistent with the view that a diagnosis of infertility does not indicate absolute sterility (8, 10). Several investigators have found that a substantial proportion of women classified as infertile eventually conceive (11–13). Thus, for our analysis, infertility reflects difficulty in conceiving during a specific period of time.

### Measurement of oral contraceptive use and other exposure variables

A detailed question on oral contraceptive use was included on the baseline questionnaire. For each year from age 13 to age in 1989, the duration of oral contraceptive use in two categories (2 to less than 10 months, ≥10 months to a full year) was recorded. Less than 2 months of oral contraceptive use was counted as noneuse. We calculated the duration of each reported interval and then summed all of the intervals to ascertain the duration of use. We categorized oral contraceptive use as ever versus never, by duration of use in four categories (never users, greater than 0 to less than 4 years, 4 to less than 6 years, ≥6 years), and by age at first use in three categories (never users, age 13–19, age 20 or greater). All three variables refer to the time period prior to the outcome event (diagnosis of ovulatory infertility among cases and first pregnancy lasting 6 months or more among controls).

The questionnaire ascertained four aspects of menstrual history (excluding time around pregnancies or when using oral contraceptives) (see table 1 for categories): cycle regularity during ages 18–22, cycle length (interval from first day of period to first day of next period), years after menses onset until cycles became regular, and age at menarche. We had no information on menstrual patterns after age 22.

We assessed the reliability of self-report of oral contraceptive history by conducting a telephone interview of 215 randomly selected participants at least 8 months after the baseline questionnaire (D. J. Hunter et al., Channing Laboratory, Harvard Medical School, unpublished manuscript). The interview used reproductive and other life events as cues for recall of contraceptive history. Of 177 nurses who reported by telephone interview that they had ever used oral contraceptives, 175 (99 percent) had reported this on the

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**TABLE 1. Characteristics of women with and without ovulatory infertility, US Nurses’ Health Study II, 1989**

<table>
<thead>
<tr>
<th>Age at event (years)*</th>
<th>Duration of oral contraceptive use prior to event (years)</th>
<th>Age at first oral contraceptive use (years)</th>
<th>Age at menarche ≥25 years (%)</th>
<th>Cycle length ≥40 days (%)</th>
<th>Cycle pattern (%)</th>
<th>Body mass index ≥29 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n = 1,917)</td>
<td>25.2</td>
<td>3.30</td>
<td>20.0</td>
<td>13.0</td>
<td>38.6</td>
<td>42.1</td>
</tr>
<tr>
<td>Controls (n = 44,521)</td>
<td>25.4</td>
<td>3.25</td>
<td>20.2</td>
<td>7.1</td>
<td>6.4</td>
<td>8.0</td>
</tr>
</tbody>
</table>

* Diagnosis of infertility for cases and pregnancy lasting ≥6 months for controls.

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baseline questionnaire. Of 38 never users by telephone interview, 37 (97 percent) reported never use on the baseline questionnaire. The mean duration of use among ever users was similar by questionnaire (mean = 54.8 months, standard deviation = 41.0 months) and telephone interview (mean = 51.8 months, standard deviation = 40.6 months) with a correlation of 0.94.

Data analysis

Since one of our aims was to evaluate adolescent oral contraceptive use as a predictor of subsequent impaired fertility, we excluded both cases and controls with an outcome event prior to age 18 (41 cases and 2,115 controls). We further excluded both cases and controls with a history of diabetes mellitus, because these women may have altered their oral contraceptive use because of their illness (36 cases and 325 controls). We further excluded those who reported use of an intrauterine device, as use of this method has been associated with increased risks of infertility (21 cases and 837 controls). Finally, after excluding those with missing values for the menstrual and hormonal factors of interest (90 cases and 1,557 controls), we found that 1,917 cases and 44,521 controls remained for analysis.

The mean duration of use and age at first use among users of oral contraceptives for cases and controls were compared using Student's t test. Logistic regression analysis was used to evaluate the following variables as confounders: age at diagnosis of infertility (cases) or age at first pregnancy lasting 6 months or more (controls), age at menarche, body mass index at age 18, ethnicity (African American, Hispanic, Asian, Caucasian, not stated), physical activity at ages 18–22, cigarette smoking status at ages from less than 15 to 19 years, and frequency of alcohol use at ages 15–22. We also controlled for menstrual cycle regularity during ages 18–22, duration between menarche and onset of cycle regularity, diagnosis of polycystic ovarian disease, and severe teenage acne, as these conditions are often treated by oral contraceptives and may, in some instances, be independently associated with ovulatory infertility. Hence, without adjustment for these conditions, one might observe a spurious association between oral contraceptive use and diagnosis of ovulatory infertility.

In addition, we used logistic models to examine several aspects of oral contraceptive use simultaneously: duration of oral contraceptive use, age at first use, and time since last use. Because the referent category was the same for all of these variables (never users), we created cross-categories by crossing each level of each variable by the other and including these in the logistic model; the group of never users was the referent stratum. A summary relative risk estimate was then calculated by using the number of women within each cross-category to weight the odds ratio for each cross-category.

Although we did assess the entire sample of women, our main analysis of interest was conducted among women with oral contraceptive use occurring greater than 2 years before the outcome event, because a short-term suppression in fertility following cessation of oral contraceptives is well established (1–7). We then conducted subgroup analyses by further excluding women with signs of menstrual/hormonal abnormality. We defined menstrual/hormonal abnormality as any one of the following: age at menarche greater than 15 years, more than 2 years after menses onset until cycle regularity, diagnosis of polycystic ovarian disease, severe teenage acne, cycle length greater than 31 days, irregular cycle length, or no periods at all during ages 18–22.

Using exposure variables from the 1989 baseline questionnaire, we calculated odds ratios as estimates of the relative risk of impaired fertility. We calculated the 95 percent confidence interval for each odds ratio (14). The p values for trend across categories of oral contraceptive use were calculated by treating the medians of each categorized level of use as a continuous variable in the logistic regression model (15).

We examined the time to subsequent conception among the cases using information about pregnancy outcome from the 1989, 1991, and 1993 questionnaires. Women were categorized according to their oral contraceptive use prior to their diagnosis of infertility. We treated the time from diagnosis of infertility to pregnancy lasting 6 months or more as the outcome of interest. We calculated the Kaplan-Meier curves for the cumulative probability of pregnancy in a year of age given that the woman had not had a pregnancy prior to that year, controlling for body mass index, cycle pattern, age at diagnosis of infertility, age at menarche, and ethnicity. The median times to pregnancy correspond to the 50th percentile of the Kaplan-Meier curve. We used multivariate Cox regression (16) to calculate the relative risk and 95 percent confidence interval of eventual pregnancy, controlling for the same covariates.

RESULTS

Women diagnosed with primary ovulatory infertility were older at menarche, had a longer interval after menses onset until regularity of cycles, had longer cycle lengths, had greater irregularity of cycle patterns, were more likely to be overweight, and were more likely to report a diagnosis of polycystic ovarian
disease than the controls (table 1). Cases and controls had a similar mean age at outcome event (25.2 and 25.4 years, respectively).

A greater proportion of cases than controls had used oral contraceptives prior to the outcome event. Among users of oral contraceptives, the mean duration of oral contraceptive use was similar, 3.3 years for cases and 3.25 years for controls ($p = 0.2$). The mean age at first use was slightly younger for cases (20.2 years) than controls (20.2 years, $p = 0.002$). The age-adjusted relative risk for ever use among the entire sample of women was 2.1 (95 percent confidence interval 2.0–2.2) (table 2). We found that physical activity at ages 18–22, cigarette smoking status at ages from less than 15 to 19, and frequency of alcohol use at ages 15–22 were not associated with the diagnosis of ovulatory infertility and, hence, we did not include these variables in the multivariate analyses. The multivariate relative risk for ever use among this sample was identical to the age-adjusted estimate.

A short-term suppression in fertility following cessation of oral contraceptives is well established; we therefore excluded women (68 percent of controls and 76 percent of cases who had ever used oral contraceptives) who had used oral contraceptives within 2 years before the outcome event (age at infertility diagnosis for cases or age at first pregnancy lasting 6 months or more for controls). After these exclusions, the multivariate relative risk for ever use was attenuated to 1.3 (95 percent confidence interval 1.1–1.5) (table 2). We found no increase in risk with increasing duration of use ($p_{\text{trend}} = 0.22$ among users only) nor with decreasing age at first use ($p_{\text{trend}} = 0.63$ among users only) (table 3). Adjusting for the time since last use had no material effect.

Menstrual factors in adolescence are important predictors of subsequent ovulatory infertility. They may also be an indication for the prescription of oral contraceptives. In young women, irregular cycles, anovulatory bleeding, oligo-ovulation, or anovulation is

<table>
<thead>
<tr>
<th>TABLE 2. Relative risks of ovulatory infertility by ever use of oral contraceptives, US Nurses’ Health Study II, 1989</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of oral contraceptives prior to event†</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Ever</td>
</tr>
</tbody>
</table>

Use of oral contraceptives among women with no oral contraceptive use within 2 years before event

| Never | 328   | 46.5 | 12,835 | 55.8 | 1.0 (referent) | 1.0 (referent) |
| Ever  | 378   | 53.5 | 10,187 | 44.2 | 1.3 (1.1–1.6) | 1.3 (1.1–1.5) |

Use of oral contraceptives among women with no signs of menstrual/hormonal abnormality‡

| Never | 69    | 18.5 | 7,406   | 29.3 | 1.0 (referent) | 1.0 (referent) |
| Ever  | 305   | 81.5 | 17,885  | 70.7 | 1.7 (1.3–2.2) | 1.6 (1.2–2.1) |

Use of oral contraceptives among women with no signs of menstrual/hormonal abnormality and with no oral contraceptive use within 2 years before event

| Never | 69    | 43.7 | 7,406   | 57.5 | 1.3 (0.9–1.8) | 1.2 (0.9–1.7) |
| Ever  | 89    | 56.3 | 5,471   | 42.5 | 1.0 (referent) | 1.0 (referent) |

* RR, relative risk.
† Multivariate relative risks were estimated from odds ratios adjusted in logistic regression for age at menarche (<11, 11–13, 14–16, ≥17 years); age at reference event; years after menarche until regularity of cycles (<2, 3–4, 5–25 years, never); cycle length at ages 18–22 (<31, 32–39, 40–59, >50 days or too irregular to estimate); cycle pattern at ages 18–22 (very regular, regular, usually irregular, always irregular, no periods); diagnosis of polycystic ovarian disease; body mass index at age 18 (<16, 16–17.9, 18–19.9, 20–21.9, 22–23.9, 24–25.9, 26–27.9, 28–29.9, 30–31.9, ≥32); severe teenage acne; ethnicity (African American, Hispanic, Asian, Caucasian, not stated).
‡ Numbers in parentheses, 95% confidence interval.
§ Excluding women with age at menarche >15 years; >2 years after menarche until cycle regularity; diagnosis of polycystic ovarian disease; severe teenage acne; and cycle length >31 days, irregular cycle length, or no periods at all during ages 18–22, as well as women with oral contraceptive use within 2 years before event.

TABLE 3. Multivariate relative risks of ovulatory infertility among women with no oral contraceptive use within 2 years before event, US Nurses' Health Study II, 1989

<table>
<thead>
<tr>
<th>Duration of oral contraceptive use prior to event†</th>
<th>Cases</th>
<th>Controls</th>
<th>Multivariate RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>328</td>
<td>12,835</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Age at first oral contraceptive use,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–19 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0—&lt;4 years</td>
<td>124</td>
<td>3,021</td>
<td>1.24 (0.99–1.57)</td>
</tr>
<tr>
<td>4—&lt;6 years</td>
<td>33</td>
<td>929</td>
<td>1.32 (0.89–1.97)</td>
</tr>
<tr>
<td>≥6 years</td>
<td>33</td>
<td>765</td>
<td>1.52 (1.00–2.30)</td>
</tr>
<tr>
<td>Age at first oral contraceptive use,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0—&lt;4 years</td>
<td>154</td>
<td>4,427</td>
<td>1.29 (1.03–1.60)</td>
</tr>
<tr>
<td>4—&lt;6 years</td>
<td>22</td>
<td>682</td>
<td>1.32 (0.82–2.13)</td>
</tr>
<tr>
<td>≥6 years</td>
<td>12</td>
<td>363</td>
<td>1.04 (0.55–1.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of oral contraceptive use prior to event§</th>
<th>Cases</th>
<th>Controls</th>
<th>Multivariate RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>328</td>
<td>12,835</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Age at first oral contraceptive use,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–19 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0—&lt;4 years</td>
<td>278</td>
<td>7,448</td>
<td>1.27 (1.16–1.39)</td>
</tr>
<tr>
<td>4–&lt;6 years</td>
<td>55</td>
<td>1,611</td>
<td>1.32 (1.18–1.48)</td>
</tr>
<tr>
<td>≥6 years</td>
<td>45</td>
<td>1,128</td>
<td>1.35 (1.18–1.54)</td>
</tr>
</tbody>
</table>

| Age at first oral contraceptive use#             |       |          |                 |
| Never used                                      | 328   | 12,835   | 1.0 (referent)  |
| 13–19 years                                     | 190   | 4,715    | 1.30 (1.18–1.44) |
| ≥20 years                                       | 188   | 5,472    | 1.27 (1.16–1.40) |

* RR, relative risk. Multivariate relative risks were estimated from odds ratios adjusted in logistic regression for age at menarche (<11, 11–13, 14–16, ≥17 years); age at reference event; years after menses onset until regularity of cycles (<2, 2–4, ≥5 years, never); cycle length at ages 18–22 (<31, 31–39, 40–50, >50 days or too irregular to estimate); cycle pattern at ages 18–22 (very regular, regular, usually irregular, irregular, no periods); diagnosis of polycystic ovarian disease; body mass index at age 18 (<16, 16–17.9, 18–19.9, 20–21.9, 22–23.9, 24–25.9, 26–27.9, 28–29.9, 30–31.9, ≥32); severe teenage acne; ethnicity (African American, Hispanic, Asian, Caucasian, not stated).

† Diagnosis of infertility for cases or pregnancy lasting ≥6 months for controls.

‡ Numbers in parentheses, 95% confidence interval.

§ Adjusted for above covariates and age at reference event.

¶ Among oral contraceptive users only.

# Adjusted for above covariates and duration of use.

often treated with combined estrogen-progestin therapy in the form of oral contraceptives (1). This could produce an artifactual association between oral contraceptives and the diagnosis of ovulatory infertility. Similarly, oral contraceptives may be prescribed to treat severe teenage acne, which itself may be a marker for a hormonal disorder.

We therefore conducted a further subanalysis excluding women with age at menarche greater than 15 years, those with more than 2 years between menses onset until cycle regularity, diagnosis of polycystic ovarian disease, severe teenage acne, cycle length greater than 31 days, irregular cycle length, or no periods at all during ages 18–22. After these exclusions and again excluding those with oral contraceptive use in the preceding 2 years, we found the multivariate relative risk to be slightly attenuated from 1.3 to 1.2 (95 percent confidence interval 0.9–1.7) for ever users (table 2). There was a suggestion, although not statistically significant, of a trend of increasing risk with increasing duration of use ($p_{trend} = 0.09$ among users only). Again, there was no statistically significant trend of increasing risk with decreasing age at first use ($p_{trend} = 0.51$ among users only) (table 4).

To examine the duration for which fertility was suppressed, we followed the cases (those diagnosed with ovulatory infertility) prospectively from the time of their diagnosis until 1993. Among the cases, 88 percent went on to have a pregnancy by 1993. Sixty-six percent of these women reported ever taking Clomid or Pergonal to induce ovulation. Since women with a history of menstrual/hormonal disorders may
have been more likely to take oral contraceptives, we focused on the subset of cases without these disorders and with no oral contraceptive use within 2 years prior to diagnosis. Seventy-seven percent of these women reported an eventual pregnancy of 6 months or greater. The median length of time to pregnancy was 2.2 years. The multivariate relative risk of eventual pregnancy for ever users of oral contraceptives as compared with never users was 1.04 (95 percent confidence interval 0.71–1.52).

**DISCUSSION**

In this large retrospective study, after allowing for the short-term suppression of fertility following cessation of oral contraceptive use and excluding women with signs of menstrual or hormonal disorder, we found a small, statistically nonsignificant, increased risk of ovulatory causes of delayed fertility for ever users of oral contraceptives. There was no statistically significant trend of increasing risk with increasing duration of use and younger age at first use. Eighty-eight percent of the cases reported an eventual pregnancy by 1993, suggesting that absolute fertility was not impaired.

Limitations of the present study warrant consideration. Entry into the cohort required registration with a state nursing board and response to a mailed questionnaire that included questions about reproductive history.

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**TABLE 4. Multivariate relative risks of ovulatory infertility among women with no signs of menstrual/hormonal abnormality* and with no oral contraceptive use within 2 years before event, US Nurses’ Health Study II, 1989**

<table>
<thead>
<tr>
<th>Duration of oral contraceptive use prior to event</th>
<th>Cases</th>
<th>Controls</th>
<th>Multivariate RR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td></td>
<td></td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Age at first oral contraceptive use,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–19 years</td>
<td>69</td>
<td>7,406</td>
<td>57.5</td>
</tr>
<tr>
<td>&gt;0—&lt;4 years</td>
<td>18</td>
<td>1,495</td>
<td>11.6</td>
</tr>
<tr>
<td>4—&lt;6 years</td>
<td>9</td>
<td>515</td>
<td>4.0</td>
</tr>
<tr>
<td>≥6 years</td>
<td>10</td>
<td>414</td>
<td>3.2</td>
</tr>
<tr>
<td>Age at first oral contraceptive use,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0—&lt;4 years</td>
<td>38</td>
<td>2,476</td>
<td>19.2</td>
</tr>
<tr>
<td>4—&lt;6 years</td>
<td>7</td>
<td>358</td>
<td>2.8</td>
</tr>
<tr>
<td>≥6 years</td>
<td>7</td>
<td>213</td>
<td>1.7</td>
</tr>
</tbody>
</table>

P_trend# = 0.09

| Age at first oral contraceptive use**           |       |          |                  |
| Never used                                      | 69    | 7,406    | 57.5             |
| 13–19 years                                     | 56    | 3,971    | 30.6             |
| ≥20 years                                       | 16    | 873      | 6.8              |
| ≥6 years                                        | 17    | 627      | 4.9              |

P_trend# = 0.51

* Excluding women with age at menarche >15 years; >2 years after menses onset until cycle regularity; diagnosis of polycystic ovarian disease; severe teenage acne; and cycle length >31 days, irregular cycle length, or no periods at all during ages 18–22, as well as women with oral contraceptive use within 2 years before event.
† RR, relative risk. Multivariate relative risks were estimated from odds ratios adjusted in logistic regression for age at menarche (≤9, 10, 11, 12, 13, 14, 15 years); age at reference event; cycle pattern at ages 18–22 (very regular, regular); body mass index at age 18 (<16, 16–17.9, 18–19.9, 20–21.9, 22–23.9, 24–25.9, 26–27.9, 28–29.9, 30–31.9, ≥32); ethnicity (African American, Hispanic, Asian, Caucasian, not stated).
‡ Diagnosis of infertility for cases or pregnancy lasting ≥6 months for controls.
§ Numbers in parentheses, 95% confidence interval.
†† Adjusted for above covariates and age at first use.
# Among oral contraceptive users only.
** Adjusted for above covariates and duration of use.
ory, weight, health, and lifestyle. It is not possible to know if response was differential between women with and without diagnosis of ovulatory infertility. However, for selection bias to have distorted these study results, women would have had to respond differentially on the basis of their oral contraceptive use history as well as their fertility. This seems unlikely, especially because infertility was a small component of this comprehensive study.

Diagnosis or detection bias is also a consideration in this study. If physicians were influenced by a woman’s contraceptive history in their performance of diagnostic tests, this may have affected our results. However, the performance of diagnostic tests for ovulatory infertility is a routine part of an infertility workup that is likely to be performed irrespective of the oral contraceptive history of the patient.

The mean age of cases and controls was 35 when they responded to the baseline questionnaire. It is possible that recall of oral contraceptive use back to age 13 could be biased by fertility status, as nurses in 1989 may have been aware of a hypothesis linking fertility to prior use of oral contraceptives. However, as this hypothesis has not received wide attention, this is unlikely.

The Nurses’ Health Study II cohort appears to be similar to the general population of US women in the frequency of ovulatory disorder infertility and the distribution of oral contraceptive use. Of the nurses whose infertility was investigated and among whom spousal infertility was excluded, 28 percent cited ovulatory disorder as the cause of their infertility; this is similar to national estimates attributing 30 percent of female infertility to ovulatory disorder (17). Eighty-three percent of the nurses report ever using oral contraceptives at baseline in 1989, comparable with national figures of 80 percent for women of the same age range (18).

Previous literature on oral contraceptives and the risk of ovulatory infertility is sparse. Bagwell et al. (19) conducted a case-control study among 419 cases of all types of primary infertility combined and 2,120 controls and found that oral contraceptive users were significantly less likely to be “infertile” as compared with nonusers (relative risk = 0.60, 95 percent confidence interval 0.42–0.86). This study had several important limitations. It was conducted predominantly among users of high dose oral contraceptives (>35 μg of estrogen) and did not collect information on whether women were trying to conceive or whether they were being treated for infertility. There was no control for menstrual factors.

Oral contraceptives inhibit hypothalamic gonadotropin releasing hormone, thereby preventing plasma gonadotropin from reaching the levels required to stimulate ovarian follicular maturation. This “hypothalamic suppression” may continue for a variable duration after cessation of oral contraceptive use in certain susceptible individuals (20). It had been widely held that conception rates for former oral contraceptive users are lower than normal for the first 3 months after stopping oral contraceptive use and returned to normal thereafter (21–23). Recently, however, several studies have found that the initial suppression of fertility can continue for a longer period. Bracken et al. (21) observed a delay in conception that continues for at least the next year among 248 former oral contraceptive users compared with 1,365 women discontinuing other methods of contraception all of whom eventually went on to conceive. The mean time to conception was 5.9 cycles (95 percent confidence interval 5.4–6.4) for former oral contraceptive users and 3.6 cycles (95 percent confidence interval 3.5–3.8) for users of other contraceptives. Since oral contraceptives are often prescribed to treat menstrual disorders, there may be a higher proportion of infertile women among oral contraceptive users. However, the finding of an increased probability of conception with increasing time since discontinuation of oral contraceptives provides evidence against this bias. These results are similar to those of Linn et al. (24), who performed a cross-sectional study among 3,214 married women with no history of infertility having planned pregnancies. The interval from cessation of contraception to conception was 13 months or greater for 24.8 percent of prior oral contraceptive users versus 10.6 percent for former users of other methods. The duration of oral contraceptive use was not statistically significantly related to the time from cessation of contraception to conception in those data.

Based on this literature, we excluded from our main analysis women who had used oral contraceptives within 2 years of diagnosis. However, the increased risk of delayed fertility among past oral contraceptive users remained. One explanation may lie in the reason for the prescription of the oral contraceptives. Cases were more likely to have menstrual irregularities in adolescence. Menstrual irregularities are often treated with oral contraceptives but are themselves important predictors of subsequent ovulatory infertility. A delay in fertility after cessation of oral contraceptives could simply be the mechanism by which women with primary amenorrhea come to medical attention. To address this issue, our final subanalysis excluded women with any signs of menstrual/hormonal abnormality in addition to those with use within 2 years before diagnosis; the risk was attenuated and no longer statisti-
cally significant. Small numbers in individual strata resulted in reduced power to examine this issue.

Our prospective analysis of the time to pregnancy among those women diagnosed with ovulatory infertility is limited because some of the women may not have continued to try to conceive after their diagnosis (e.g., their marital status may have changed). Hence, the 88 percent of women who did eventually go on to conceive is an underestimate of the true subsequent fertility of this population. In this group, we found no difference in the probability of eventual pregnancy of 6 months or greater by prior use of oral contraceptives.

Our study found that ever use of oral contraceptives was associated with a small, statistically nonsignificant, increased risk of ovulatory causes of delayed fertility 2 years after oral contraceptive cessation after controlling for menstrual and hormonal irregularity, which are often clinical indicators for the prescription of oral contraception. The fact that over 80 percent of the cases reported an eventual pregnancy suggests that absolute fertility was not impaired.

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