ORIGINAL ARTICLE: CONTRACEPTION

The influence of prior oral contraceptive use on risk of endometriosis is conditional on parity

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Objective: To estimate the influence of prior oral contraceptive pill (OCP) use on future diagnosis of endometriosis in young women.
Design: Prospective cohort study, the Australian Longitudinal Study on Women's Health.
Setting: Community-based sample.
Patient(s): 9,585 women age 18–23 at study onset.
Intervention(s): None.
Main Outcome Measure(s): Risk of self-reported endometriosis estimated with Cox proportional-hazards regression with time-dependent covariates.
Result(s): Compared with never users, endometriosis hazard ratios in nulliparous women with <5 years and ≥ 5 years of OCP use (preceding diagnosis) were 1.8 (95% CI, 1.30–2.53) and 2.3 (95% CI, 1.59–3.40), respectively. Similar risk was seen in both women reporting infertility and unsure fertility. In parous women with <5 years of use, the hazard ratio for endometriosis was 0.41 (95% CI, 0.15–0.56) and for ≥ 5 years of use was 0.45 (95% CI, 0.16–1.23). Women reporting early noncontraceptive OCP use had a twofold higher risk (odds ratio 2.07; 95% CI, 1.72–2.51).
Conclusion(s): Prior OCP exposure reduces the risk of diagnosis of endometriosis in parous women but increases it among nulliparous women; these associations appear unaffected by fertility status. An increased risk of endometriosis diagnosis seen in women reporting early noncontraceptive OCP use may explain some of the positive OCP risk seen in nulliparous women. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Combined oral contraceptives, dysmenorrhea, endometriosis, risk factor

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Endometriosis is a serious women's health problem that affects between 5% and 10% of reproductive-aged women. These ectopic uterine implants are linked to sex hormone-mediated inflammation and are a common cause of female pelvic pain and infertility due to injury of peritoneal tissues (1). Endometriosis has become a significant public health issue, costing approximately $22 billion annually in U.S. health-care dollars and lost wages/productivity (2). Although oral contraceptive pills (OCPs) are frequently used to treat these

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patients, the literature is not consistent as to whether prior OCP use is protective against future development of endometriosis when given to healthy asymptomatic women. In favor of the possibility of protection is the theory that prior exposure to exogenous hormones may reduce the cumulative amount of endometrial tissue presented to the peritoneal cavity via retrograde menstruation (3). Furthermore, OCP exposure has been shown to inhibit endometriosis development in a chicken model of this gynecologic condition (4). Oral contraceptive pills also appear to protect women from other hormonally mediated problems, such as dysmenorrhea, heavy menstrual bleeding, ovarian cysts, and endometrial cancer (5,6). One recent meta-analysis has shown the opposite for endometriosis and suggests the possibility of increased endometriosis risk with prior OCP exposure (7).

The Australian Longitudinal Study on Women's Health (ALSWH) represents a unique opportunity to address the question of whether OCPs are associated with higher or lower rates of endometriosis. This large prospective, observational cohort study is tracking a wide variety of reproductive health factors and is an ideal platform to estimate the association between OCP use and risk of endometriosis.

MATERIALS AND METHODS

We analyzed the data obtained from participants in the Australian Longitudinal Study on Women's Health (ALSWH). The ALSWH was established to investigate an extensive battery of women's health issues over a 20-year period (1996–2016). Women were recruited into three separate cohorts (18–23 years, 45–50 years, and 70–75 years) in 1996, by random selection from the national health insurance database, which includes all permanent residents of Australia. An overrepresentation of women living in rural and remote areas was planned (8). Further details of recruitment, response rates, and surveys can be found at http://www.alswh.org.au. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Ethics clearance for the parent study was obtained from the University of Newcastle, Australia. This report focuses on the youngest cohort (aged 18–23 years at baseline in 1996) as these women are at the highest risk for a new diagnosis of endometriosis during the period of observation. We analyzed data from surveys completed in 1996, 2000, 2003, and 2006. There are over 300 variables available from the questionnaires, so we evaluated only those items known to be associated with endometriosis.

Our goal was to assess whether there was an association of OCP use (primary predictor) preceding a new diagnosis of endometriosis (outcome). Because the surveys assess the diagnosis of endometriosis any time over a 3- or 4-year window, whereas OCP use is characterized at a cross-sectional assessment anchored at the time of survey completion, we assessed OCP use up to the survey preceding the one where endometriosis status was queried. Thus, we modeled the relationship by using survey 1 (1996) OCP use to predict endometriosis at surveys 2 (2000), 3 (2003), or 4 (2006), with survey 2 OCP use to predict endometriosis at survey 3 or 4, and with survey 3 OCP use to predict endometriosis at survey 4. In this study, OCP use duration is a cumulative estimate reported by the women at each survey (in years), whereas other covariates such as marital status, body mass index (BMI), education, and depression are cross-sectional in their time frame. In the univariate analysis, we compared baseline (survey 1) demographic and health characteristics of women with and without endometriosis diagnosed subsequently at survey 2, 3, or 4, including global health measures such as the Short Form 36 Health Survey (SF-36), which has been widely used in survey research to assess quality of life, mood profiles, prior pregnancy history, and smoking/alcohol exposure. A global somatization score was calculated by summing the scores (Likert items 0–3 corresponding to "no," "rarely," "sometimes," "often") from the general symptom screen (encompassing items such as tiredness, allergies, constipation, skin issues, totaling 51 [17 subitems] in survey 1, and 57 [19 subitems] for surveys 2–4). Complete coding of variables is listed in Table 1.

The primary outcome was self-reported diagnosis of endometriosis. Surveys 2, 3, and 4 each included a question about endometriosis. The survey 2 questions asked whether "a doctor has ever told you that you have [endometriosis]" [in the last 4 years] or [more than 4 years ago]. We limited analysis to incident cases (endometriosis diagnosed for the first time during the last 4 years on survey 2). The survey 3 and 4 questions asked, "Have you been diagnosed or treated for [endometriosis] in the last 3 years?" The primary independent variable was self-reported oral contraceptive pill (OCP) use.

Surveys 2, 3, and 4 each included a question about cumulative OCP use: "For how many years in total have you EVER taken the oral contraceptive pill?" The risk window for OCP exposure was based on self-report from the epoch prior to that in which the diagnosis of endometriosis was made. Cumulative exposure to OCP was reported slightly differently across the four surveys, and a decision was made to subsequently stratify this time-varying covariate for analysis as never, less than 5 years of exposure, and equal to or greater than 5 years. Person-years at risk were calculated based only on participants who completed at least the first two surveys to accurately ascertain the incident time frame for this calculation. Recognizing that self-report of endometriosis diagnosis by a physician may not be precise, a sensitivity analysis was conducted using a more restricted definition of endometriosis, which only included those women with both a positive self-report of endometriosis and also self-reported concomitant severe period pain as "sometimes" or "often."

Differences between groups were tested using Pearson and Mantel-Haenzel chi-square tests for nominal and ordinal variables and two-sample *t*-tests for continuous variables in univariate analysis. Both univariate and multivariable time-varying Cox regression analysis were conducted. Confounders and effect modifiers were determined by extensive review of the literature and statistical analyses. Potential confounders (with final collapsed coding where appropriate) included area of residence (urban, rural, remote), education ($<$ high school [H.S.], H.S. certificate, $>$ H.S.), marital status (never, married, other), parity (0, 1, $>$1), BMI (kg/m^2 categorized as underweight [$<$18.5], acceptable [$\geq$ 18.5 and $<$ 25], overweight [$\geq$ 25 and $<$ 30], or obese [$>$30]), annual income