In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study

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Objective: To assess in utero exposures and the odds of an endometriosis diagnosis.
Design: Matched cohort design.
Setting: Fourteen participating clinical centers in geographically defined areas in Utah and California.
Patient(s): Operative cohort comprised 473 women undergoing laparoscopy/laparotomy, and an age- and residence-matched population cohort comprising 127 women undergoing pelvic magnetic resonance imaging (MRI), 2007–2009.
Intervention(s): None.
Main Outcome Measure(s): Women completed standardized interviews before surgery or MRI regarding in utero exposures: mothers' lifestyle during the index pregnancy, and the index woman's gestation and birth size. Endometriosis was defined as visually confirmed disease in the operative cohort, and MRI visualized disease in the population cohort. The odds of an endometriosis diagnosis and corresponding 95% confidence intervals (CI) were estimated for each exposure by cohort using logistic regression and adjusting for current smoking, age at menarche, body mass index, and study site.
Result(s): Endometriosis was diagnosed in 41% and 11% of women in the operative and population cohorts, respectively. In the primary analysis, adjust odds ratios (AORs) were elevated for maternal vitamin usage (1.27; 95% CI, 0.85–1.91), maternal cigarette smoking (1.16; 95% CI = 0.61–2.24), and low birth weight (1.1; 95% CI, 0.92–1.32). Reduced odds were observed for maternal usage of caffeine (0.99; 95% CI, 0.64–1.54), alcohol (0.82; 95% CI, 0.35–1.94), paternal cigarette smoking (0.72; 95% CI, 0.43–1.19), and preterm delivery (0.98; 95% CI, 0.47–2.03). Sensitivity analyses mostly upheld the primary results except for a decreased AOR for preterm birth (0.41; 95% CI, 0.18–0.94) when restricting to visualized and histologically confirmed endometriosis in the operative cohort.
Conclusion(s): In utero exposures were not statistically significantly associated with the odds of an endometriosis diagnosis in either cohort. (Fertil Steril® 2013;99:790–5. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, epidemiology, in utero, ovarian dysgenesis hypothesis

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The Barker hypothesis (1) sparked considerable interest in the potential early origins of health and disease (2). This hypothesis posits that early exposures, including those arising from parents' lifestyles during sensitive windows of human development such as pregnancy, may permanently reprogram the developing embryo or fetus for extrauterine life. This reprogramming is speculated to occur largely through epigenetic

mechanisms (3). Such reprogramming of human fecundity, defined as the biologic capacity of men and women for reproduction irrespective of pregnancy intentions, has also been observed to include early environmental exposures with transgenerational effects (4, 5).

In response to the early origins of health and disease hypothesis, investigators have assessed in utero exposures in adult women with endometriosis. Higher odds of an endometriosis diagnosis were associated with in utero diethylstilbestrol (DES) (6) exposure, and lower odds of the diagnosis with in utero exposure to cigarette smoking (7) and increased birth weight (6). Other evidence suggestive of an early origin for endometriosis includes body size. Hediger et al. (8) first reported that women eventually diagnosed with endometriosis tracked leaner from childhood through diagnosis relative to women without endometriosis. This finding was subsequently corroborated in the large Nurses Health III Cohort Study (9). Despite an evolving body of evidence suggestive of an early origin for endometriosis, current studies have been limited by the fact that the endometriosis was only self-reported (instead of the gold standard of visualized disease) (6) and that the woman with endometriosis had to retrospectively recall their mother's exposures and behaviors during pregnancy (6, 7). We designed the Endometriosis, Natural History, Disease, Outcome (ENDO) Study, in part, to specifically assess in utero exposure, gestation, birth size, and endometriosis, while attempting to address some of the methodologic challenges of endometriosis research (10).

MATERIALS AND METHODS

Study Design and Cohorts

Full human subjects approval obtained for this study (Committee of Human Research, University of California–San Francisco; Institutional Review Board, University of Utah; Intermountain Healthcare Office of Research, Utah; and the National Institutes of Health Institutional Review Board Reliance). Each of the women provided informed consent before any data collection. The ENDO Study used a matched exposure cohort design in which an operative cohort was matched to a population cohort. The operative cohort comprised women scheduled for laparoscopy or laparotomy at one of 14 participating clinical sites in the Salt Lake City and San Francisco areas. Subsequently, the operative cohort was matched to the population cohort comprising women residing within a 50-mile radius surrounding the 14 participating centers. By design, the population cohort was not seeking surgery but was at risk for endometriosis and its diagnosis, and eligible women had to be currently menstruating and residents in the geographical areas served by the clinical sites.

Given the absence of uniform sampling frameworks to find women at risk for endometriosis and its diagnosis, we used the Utah Population Registry for our Utah clinical sites, a sampling framework that represents approximately 95% of the state's residents (11), and a well-established household sampling database for California (Marketing Systems Group, http://www.m-s-g.com/web/genesys/index.aspx). Letters were sent to all women in the population sampling frameworks introducing the study, followed by telephone calls to screen women for eligibility: [1] no history of laparoscopically confirmed endometriosis; [2] currently menstruating; [3] resident within the geographic clinical catchment areas; [4] aged 18 to 44 years; [5] not currently breastfeeding for $\geq$6 months; [6] no injectable hormonal treatment within the past 2 years; and [7] no history of cancer (except nonmelanomatous skin cancer). The same criteria were used for the operative cohort.

The age criterion was intended to reflect the female reproductive age distribution with the exception of age extremes (adolescents and perimenopausal women) and to allow sufficient time for women to become exposed to environmental agents. The breastfeeding criterion was intended to prevent a reduction in the woman's serum concentration of lipophilic environmental chemicals via lactational transfer.

All women in the operative cohort underwent surgery, and all women in the population cohort underwent pelvic magnetic resonance imaging (MRI) for the diagnosis of endometriosis using a standardized protocol. The operative and population cohort comprised 473 and 127 women with complete information on endometriosis status, respectively. Complete details of the ENDO Study methodology are provided elsewhere (10).

Data Collection

Upon enrollment, all women were interviewed before surgery or MRI regarding their knowledge of exposures while in utero. Specifically, women were asked about parental smoking during pregnancy (yes/no), mother's use of alcohol (yes/no), caffeinated beverages (yes/no), and vitamins (yes/no), and whether the mother received diethylstilbestrol (DES) or infertility treatment for the index woman's pregnancy. In addition, women were asked the plurality of their birth (singleton/multiple) along with their birth weight (pounds and ounces), birth length (inches), and length of gestation (categorized as $<$37, 37–42, or $>$42 weeks). Standardized anthropometric protocols were used to measure height and weight (12). Surgeons completed standardized operative reports for all women in the operative cohort to capture the primary postoperative diagnosis and any other operative findings.

Endometriosis was defined as consistent with the gold standard for surgically visualized disease (13). Given the observational study design, endometrial implants were removed for histologic assessment per the surgeon's standard of practice. Histologically confirmed disease was assessed in the sensitivity analyses. Severity of endometriosis was staged according to Revised American Society for Reproductive Medicine (ASRM) criteria (14). A primary MRI endometriosis diagnosis, largely comprising ovarian endometriomas, was determined and corroborated by the study's two radiologists who were blinded to exposure and disease status. All other MRI findings were noted as well, including adenomyosis. As defined a priori, we restricted endometriosis in the population cohort to represent the primary diagnosis.

Statistical Analysis

Descriptive analyses included the inspection of missing data by cohort, exposure, and disease status followed by