Potential influence of in utero and early neonatal exposures on the later development of endometriosis

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Objective: To investigate the possible correlation between maternal characteristics, in utero and early neonatal life exposures, and the development of endometriosis in adult life.
Design: Case-control study.
Setting: University hospital.
Patient(s): A group of 161 patients with endometriosis and a control group of 230 women undergoing laparoscopy for benign adnexal diseases and free of endometriosis.
Intervention(s): All women included in the study were requested to answer a series of questions about their mothers' gestational data and on their own perinatal and early postnatal lives.
Main Outcome Measure(s): Odds ratio, adjusted odds ratios, and 95% confidence intervals for the associations between maternal characteristics during the patient's pregnancy, in utero exposure to obstetrical and perinatal complications, and the type of feeding received during the neonatal period with the development of endometriosis in adult life.
Result(s): Mothers of women with endometriosis were significantly more likely to be affected by endometriosis or uterine fibroids, with a higher incidence of smoking during pregnancy. Women with endometriosis were more frequently born prematurely, with a significantly lower birth weight, and their mothers experienced preeclampsia during their pregnancies more often than control subjects. They were also more frequently formula fed than breast fed in early life. However, only prematurity and formula feeding were retained in the multivariate analysis model.
Conclusion(s): Among intrauterine and early neonatal exposures, prematurity and formula feeding were risk factors for the development of endometriosis in adult life. Further studies should evaluate the underlying biologic mechanisms. (Fertil Steril® 2016;105:997–1002. ©2016 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, preterm birth, low birth weight, formula feeding, epigenetic

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Endometriosis is a common benign gynecologic disease of reproductive-age women, characterized by alterations of estrogen and progesterone receptors and affecting inflammatory pathways (1, 2). Genetic and epigenetic factors play a major role in the pathogenesis (3), as confirmed by family and twin studies demonstrating a heritability model similar to complex diseases (4). Several studies are looking for possible risk factors influencing the increased incidence of endometriosis. Nulliparity, short menstrual cycle length, and early menarche are associated with endometriosis (5–7). Women with endometriosis have a low body mass index (BMI) (8–10) and are more likely to be exposed to environmental factors such as pesticides and plasticizers (11), whereas cigarette smoking does not influence the development of the disease (12, 13).

The increased incidence of endometriosis over the past decade is explained in part by a higher diagnostic competence, but also by a real augmentation of risk factors (14), even though there is no clear link to specific causes. In medical science it is becoming clear that early exposures, both in utero

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and in neonatal life, may permanently reprogram the developing embryo or fetus for extrauterine life (15). A classic example is the increased incidence of endometrial cancers in women delivered by pregnancies whose mothers used diethylstilbestrol (DES) as an antiemetic drug (16). An 80% increase in the rate of endometriosis was also described in women whose mothers used DES in pregnancy (17). Indeed, a linear increase in the incidence of the disease with decreasing birth weight has been reported (18, 19). Therefore, the epigenetic imprinting of genes during development may have a critical role in the adult female reproductive tract function (20).

The aim of the present study was to further investigate in a more recent group of patients the possible correlation between in utero and early neonatal life exposures and the later development of histologically confirmed endometriosis.

MATERIALS AND METHODS

A case-control study was conducted from January to December 2014 in the Department of Molecular and Developmental Medicine, University of Siena, and in collaboration with a nonprofit association of women with endometriosis, "A.P.E." Onlus. The study was approved by the Institutional Review Board of the University of Siena. The study population comprised a group of women referred to our center for endometriosis as case subjects. Women with histologically confirmed endometriosis, made for the first time from 2004 to 2013, were included. A control group was recruited among women undergoing a laparoscopy, during the same study period, for benign adnexal diseases (ovarian cysts, hydrosalpinx, pelvic inflammatory disease) and who were free of endometriosis. Inclusion criteria for both case and control subjects were: 1) Caucasian origin; 2) Italian citizenship; 3) age 21–45 years; and 4) mother alive and able to give information about her gynecologic and obstetrical history.

A total of 436 women were recruited to the study and were requested to answer a series of questions about their mothers' gynecologic and obstetrical data and their own perinatal and postnatal data. The questionnaires were administered by two interviewers. Before the recruitment, patients were informed that the study focused on the link between intrauterine life and the development of chronic adult diseases, but they were blinded to the specific goal related to endometriosis. Maternal variables included age at delivery, parity, and the presence of hormonal or uterine disorders (endometriosis, uterine fibroids, polycystic ovarian syndrome [PCOS]). Gestational factors included single versus multiple gestation, spontaneous versus assisted reproductive technology conception, obstetrical complications (including antepartum bleeding), preeclampsia, preterm birth, use of drugs, and smoking during pregnancy, bed rest. Perinatal factors included gestational age at delivery, mode of delivery, postpartum hemorrhage, birth weight, low birth weight (LBW; $<$2,500 g), very low birth weight (VLBW; $<$1,500 g) and macrosomia (birth weight $>$4,000 g). Postnatal factors included breastfeeding or formula feeding. The questionnaire was administered in the presence of patients' mothers, or, if not attending the interview, they were contacted by telephone to retrieve missing information or confirm the reported data. A process of data validation by reviewing the patients' medical notes and their mothers' case notes was conducted, requesting mothers' case notes when gestational abnormalities had been reported. All cases lacking a validated review and those where the patient's mother could not be contacted by telephone were excluded from the analysis. Accordingly, 45 patients (15 case and 30 control subjects) were excluded from the study because of missing (n = 18) or not validated (n = 27) data.

A total of 391 women were included in the analysis: 1) endometriosis group (n = 161); and 2) control group (n = 230). The mean ± SD age (35.29 ± 7.08 vs. 33.10 ± 5.73 years) and the BMI (23.04 ± 3.7 vs. 22.94 ± 3.01 kg/m^2) were similar between the two groups. Based on clinical and histologic findings, endometriotic lesions were classified into superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA), deep infiltrating endometriosis (DIE), mixed OMA plus SUP, and mixed OMA plus DIE, according to the revised American Fertility Society classification. In the endometriosis group, all women underwent surgery: 64% had one surgical intervention, 19% underwent two interventions, while 17% had three or more interventions. Based on localization of endometriotic lesions, 24% of women were diagnosed as OMA, 21% DIE, 48% mixed OMA plus DIE, 5% mixed OMA plus SUP, and 2% SUP.

Statistical Analysis

All data were analyzed with the use of Graphpad Prism version 5.00 for Windows statistical software. Data were coded or recoded for analysis when required. Demographic, maternal, gestational, perinatal, and postnatal variables were compared between case and control subjects. For this univariate analysis, binomial variables were compared by means of chi-square test or Fisher exact test, or binominal logistic regression as appropriate, and odds ratios (ORs) and 95% confidence intervals (CIs) were recorded. Unpaired *t* test or Mann-Whitney *U* test was used as appropriate for quantitative variables. A *P* value of $<$.05 was considered to be statistical significant. Afterward, multivariate models including significant variables were adjusted for maternal history of endometriosis and uterine fibroids, maternal age, and smoking to calculate adjusted ORs of variables retained in the model.

RESULTS

Mothers of women with endometriosis were significantly more affected by endometriosis (*P*=.0006) or uterine fibroids (*P*$<$.001; Table 1). During gestation higher incidences of preeclampsia (*P*=.0094), preterm birth (*P*$<$.001), and cigarette use (*P*=.04) were found in women delivering a female child who later developed endometriosis (Table 1).

The birth weight of women with endometriosis was significantly lower than that of control subjects (*P*=.0010), with a higher rate of LBW neonates (*P*=.0063). Women with endometriosis in adult life were more frequently formula fed in early life than breast fed (*P*=.0001; Table 1). There was no association with severity of disease, number of surgical