Heritability of endometriosis

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Objective: To estimate the relative contribution of genetic influences and prevalence on endometriosis.
Design: Analysis of self-reported data from a nationwide population-based twin registry.
Setting: Not applicable.
Patient(s): A total of 28,370 women, female monozygotic (MZ) or dizygotic (DZ) twins, who participated in either of two surveys (1998–2002 or 2005–2006).
Intervention(s): None.
Main Outcome Measure(s): Self-reported endometriosis, validated by medical records.
Result(s): A history of endometriosis was reported by 1,228 female twins. The probandwise concordance was 0.21 for MZ and 0.10 for DZ twins. Higher within-pair (tetrachoric) correlation was observed among MZ (0.47) compared with DZ (0.20) twins. The best-fitting model revealed a contribution of 47% by additive genetic factors and the remaining 53% attributed to unique environmental effects.
Conclusion(s): Our findings suggest both genetic and unique (nonshared) environmental influences on the complex etiology of endometriosis and support the hypothesis that genes have a strong influence on phenotypic manifestations of endometriosis. (Fertil Steril® 2015;104: 947–52. ©2015 by American Society for Reproductive Medicine.)

Key Words: Concordance, endometriosis, heritability, twins

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Endometriosis is one of the most common benign gynecologic diseases and is characterized by the presence of ectopic endometrial tissue outside the uterus (1). Most estimates of prevalence have been made on the basis of surgical populations or small samples and are therefore highly selective. These estimates range between 2% and 10% in women of reproductive age, and the proportion can be up to 50% among infertile women (2–4). Although the etiology and pathogenesis of endometriosis remain largely unknown, there is mounting evidence that it is a complex multifactorial disease with both genetic and environmental components contributing to disease susceptibility (4).

Studies on heritability—the presence of variance accounted for by genetic factors—have demonstrated familial accumulation (5–7), increased concordance in monozygotic (MZ) twins (4), and a 3 to 15 times higher risk in first-degree relatives of women with endometriosis compared with those in the general population (8–11). In an Australian twin-based study, a twofold increase in endometriosis risk in MZ compared with dizygotic (DZ) twin pairs was reported (4), which supports that the genetic component contributing to phenotypic variability in endometriosis is about 50% (4, 12). These and other findings on heritability have served as a platform for identification of susceptibility loci and also identification of potential candidate genes using a genomewide association study strategy in populations of European descent (13, 14) and in Japanese populations (15, 16). One study showed that heritability is also apparent in nonhuman primates (17). These data imply that endometriosis is a complex genetic trait and indicate that a number of genes interact with each other to form disease susceptibility, with the phenotype emerging in the presence of environmental risk factors. However, there is no evidence as yet of the

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type of environmental contribution. Chemicals in our environment as well as in food have been discussed as possible contributing factors (18–20).

Only one study so far has used quantitative analysis to examine the contribution of genetic and environmental factors on endometriosis using a small twin sample (4). A larger twin sample is predicted to provide further consistency to the quantitative estimation of genetic and environmental factors. No estimates of the genetic contribution to individual differences among the Swedish population have been reported to date. Our study estimated the prevalence of endometriosis in a large sample of female twins aged 20 to 65 years and the heritability to endometriosis susceptibility using data from the population-based Swedish twin registry.

MATERIALS AND METHODS

Data Sources

Data from two cross-sectional surveys were used: the Screening Across the Lifespan Twin (SALT) study (1998–2002) directed to twins born before 1959 and aged 40 years or older (21) and the Swedish Twin Study of Adults' Genes and Environments (STAGE) (2005–2006) which included twins born from 1959 to 1985, aged 20 to 40 years (22). The data collection process included a detailed set of questions pertaining to women's health, and one question specifically related to endometriosis.

Participants

The cohort comprised 38,154 female twins who had responded to the questionnaires in either SALT or STAGE. The women were asked, "Have you ever been diagnosed with endometriosis, also called chocolate cysts?" Female twins over 65 years of age (n = 9,784) did not receive the question on endometriosis and were therefore excluded. In total, 28,370 women responded to the question, out of which 1,228 responded positively. There were 3,595 MZ and 3,601 DZ female twin pairs, where both twins had answered the question on endometriosis. For the analysis of heritability, all 7,196 complete twin pairs and 13,978 single female twins (where cotwin did not respond) were included. The details are shown in Figure 1.

Validation of Self-reported Data and Twin Status

We mailed letters in 2010 to all twins with a self-reported endometriosis diagnosis who were still alive to obtain written consent to scrutinize their medical records. Of the 1,228 women, 60% gave consent. A letter was then sent to the heads of the departments of obstetrics and gynecology of all pertinent hospitals and private gynecologic outpatient clinics in Sweden to obtain a copy of the medical records. Reminders were sent, and the departments were contacted by phone after 6 to 8 weeks if the medical records has not been received. We received 442 medical records.

A structured protocol was used to record the information that was gathered from the medical records. Visible typical endometriosis lesions in surgery, histologic reports, and/or evidence of clinical diagnosis (medical history, clinical examination, and/or sonography) were accepted as evidence of diagnosis. One of the authors (R.S.) examined all the medical records, while another author (M.O.) examined 20 randomly selected medical records; there was 100% agreement between the two authors.

Zygosity was assigned on the basis of a series of questions about intrapair similarities in childhood, which has been validated repeatedly with serologic markers showing 98% or higher accuracy (23). The study was reviewed and approved by the regional ethics committee in Stockholm, Sweden (DNR 2009/1676–31/2).

Statistical Analysis

Age was presented as mean and ± standard deviation. The prevalence of endometriosis with 95% confidence interval (CI) based on normal approximation was calculated as the proportion of individuals with self-reported endometriosis among all women included in the study.

Probandwise concordance (i.e., the risk of endometriosis for the cotwin of a twin with endometriosis) was estimated by using 2×2 contingency tables for MZ and DZ twin pairs and the formula $2K/(2K + D)$, where K is the number of concordant twin pairs and D is the number of discordant twin pairs as regards endometriosis (24). Correlation of liability (tetrachoric or within-pair correlation) was also estimated for each zygosity group (25). Higher concordance rates and correlations of liability in MZ than in DZ twins indicate a genetic contribution to the manifestation of disease. Shared environmental influences were implied if the DZ correlation was greater than half the MZ correlation. Statistical analysis was conducted using Stata IC 12 and R software version 3.1.1.

Genetic Modeling

Quantitative genetic modeling was used to investigate the heritability of endometriosis. Following the classic twin design, we allowed the variation in the population to be due to additive genetic factors (A, the narrow sense heritability), environmental factors shared between twins in pairs (C), and environmental factors unique to an individual (E) (26). Because MZ twins are genetically identical, A was assumed shared to 100% between twins in a pair, and in DZ twins it was assumed to be shared to 50% because on average they share half of their cosegregating alleles. In both MZ and DZ twin pairs, C was assumed to be shared to 100%, and E was assumed nonshared. Because endometriosis is a binary trait, we used the liability-threshold approach in analyzing the data: each individual is assumed to have an underlying normally distributed liability of having the disease, with 0 observed if the liability is lower than an estimated threshold, and 1 observed if it is above the threshold (27).

Using these assumptions, we fitted structural equation models to raw binary data using the package OpenMx, version 1.4-3060 (28), in the statistical software R, version 3.1.1. We started by fitting a model including A, C, and E sources of variance, called an ACE model. We then fitted restricted models (AE, CE, and E), where the letters indicate which sources were allowed to contribute to the variation. The restricted models were compared with the full ACE model using likelihood ratio tests to identify which sources