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## Epidemiology of endometriosis and its comorbidities

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### ABSTRACT

Genetic profile, inflammation, hormonal activity, menstrual cyclicity, organochlorine burden, prostaglandin metabolism and immunological factors have been suggested to play a role in the establishment and development of endometriosis. From the epidemiological perspective, several risk factors have been studied to suggest or support the different aetiological hypotheses.

Social class and family history apart, the factors most consistently associated with endometriosis are early age at menarche, and long and heavy menstrual cycles. These menstrual characteristics (together with nulliparity) reflect increased exposure to menstruation. The other main risk factors are pigmentary traits and sun habits, alcohol intake, use of oral contraceptives, and environmental factors such as exposure to polychlorinated biphenyls and dioxin. All of these factors support a potential role of hormonal milieu and inflammation in the pathogenesis of endometriosis.

There is a clear association between endometriosis and gastrointestinal and immunological diseases, ovarian cancer and other gynaecological cancers, and thyroid cancer.

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### Introduction

Endometriosis is a benign, gynaecological disease. It is estimated to affect approximately 7–10% of women, with clinically relevant conditions affecting approximately 3% of women of fertile age [1,2].

Various factors have been suggested to play a role in the establishment and development of endometriosis. These include genetic profile, inflammation, hormonal activity, menstrual cyclicity, organochlorine burden, prostaglandin metabolism and immunological factors.

From the epidemiological perspective, several risk factors have been studied to suggest or support the different aetiological hypotheses. In recent years, great efforts have been made to analyze the association between endometriosis and other pathological conditions in order to offer further insight into the pathogenetic mechanisms, or to identify women at risk [3].

This paper synthesizes the evidence from epidemiological studies with regard to risk factors and comorbidities, but does not consider associations between endometriosis and ovarian, breast, endometrial, melanoma and thyroid cancers. These associations have been discussed elsewhere [3].

### Methods

MEDLINE (1985–2011), EMBASE (1985–2015) and Science Citation Index Expanded (1985–2015) were searched to identify relevant epidemiological studies on risk factors for endometriosis. The search terms included 'endometriosis' in combination with: 'epidemiology', 'risk factors', 'menstrual factors', 'parity', 'diet', 'smoking', 'alcohol', 'autoimmune disease', 'rheumatoid arthritis', 'asthma', 'atopic disease', 'inflammatory bowel disease', 'coeliac disease' and 'cardiovascular disease'. All pertinent reports were retrieved, and the reference lists were searched systematically in order to identify any potential additional studies that could be included. Only studies that were published as full-length articles and in the English language were considered.

In the preparation of this article, meta-analyses/systematic reviews were considered as the main source of evidence.

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**Results**

**Table 1** summarizes the main risk factors for endometriosis, and the strength of associations found in the published studies. Each risk factor is discussed briefly below.

*Sociodemographic characteristics*

*Socio-economic status/occupational level*

Many early epidemiological studies on risk factors for endometriosis showed increased frequency of the disease among women of higher socio-economic status/higher occupation level [4,5]. This association was traditionally explained by diagnostic bias: for example, women of higher socio-economic status may be more aware of health problems. Furthermore, socio-economic status may be associated with many of the risk factors suggested for endometriosis. For example, reproductive pattern, body mass, physical activity and diet are all associated with education and socio-economic status [6]. Thus, socio-economic status and education are indicators of lifestyle habits that are associated with increased risk of endometriosis.

However, the association between socio-economic status and endometriosis may be more complex. For example, it has been suggested recently that women who work rotating nightshifts for ≥5 years may have a modestly elevated risk of endometriosis if they are concurrently infertile [7].

*Family history*

There is consistent evidence that a family history of endometriosis is more common in women with the disease [8]. The first-degree relatives of affected women are at three- to nine-fold higher risk of developing the disease. Potential bias has been suggested to explain, at least in part, this association, as women with a family history of the disease may be more prone to undergo medical testing. However, twin studies have shown that heritability accounts for the development of endometriosis to a similar extent as other complex genetic diseases [9]. Familial aggregation of endometriosis suggests a genetic contribution to the disease, and some genetic factors have been identified in genome-wide association studies [10].

**Table 1**  
Recognized risk factors for endometriosis.

Risk factor	Strength of association
Socio-economic status	↑, limited study
Family history	↑↑
Constitutional factors	
Weight	↓, inconsistent
Peripheral body fat distribution	↑, limited study
Pigmentary traits and sun habits	↑, limited study
Personal habits	
Diet	↓, limited study
Physical activity	↓, limited study
Smoking	↑=, limited study
Alcohol intake	
Reproductive and gynaecological factors	
Age at menarche	↑↑, consistent
Menstrual cycle length	↑↑, consistent
Duration of flow	↑, limited study
Parity	↓↓, consistent
Contraception	
Oral contraceptive use	inconsistent
Environmental factors	
Exposure to polychlorinated biphenyls and dioxin	↑, limited study/inconsistent
Comorbidities	
Gastrointestinal diseases	↑, limited study
Immunological diseases	↑, limited study
Cardiovascular diseases	↑, limited study

*Reproductive and gynaecological factors*

*Age at menarche, menstrual cycle length, duration of flow and parity*

Epidemiological studies since the 1980s have focused on the role of reproductive, menstrual and hormonal factors [4,11,12]. Early age at menarche, and long and heavy menstrual cycles has been associated consistently with endometriosis. These menstrual characteristics (together with nulliparity) reflect increased exposure to menstruation [13], and provide strong support for the reflux hypothesis. Parity may also lower the risk of endometriosis, as the high progesterone level associated with pregnancy may impair the establishment or development of the disease.

*Contraception*

Combined oral contraceptives (OCs) reduce the volume of menstrual flow substantially, and may hypothetically interfere with implantation of refluxed endometrial cells. Women taking OCs have regular menstrual flow and generally experience a greater number of flows over 1 year than women not taking OCs. Also, OCs contain progestins that may counteract the effect of oestrogens in endometriosis, and progestins are a recognized treatment for the disease.

A meta-analysis published in 2010 considered 18 studies on the issue: six cross-sectional studies, seven case-control studies and five cohort studies. Pooling the results derived from all the included reports, independent of study design, yielded a common relative risk of 0.63 [95% confidence interval (CI) 0.47–0.85] for current OC users, 1.21 (95% CI 0.94–1.56) for past OC users and 1.19 (95% CI 0.89–1.60) for ever OC users. The authors indicated that methodological drawbacks, such as uncertain temporal relationships between exposure and outcome in cross-sectional studies, and suboptimal selection of controls in case-control studies, limit the quality of the available evidence [14].

The reduced risk of endometriosis during OC use may be, at least in part, due to postponement of surgical evaluation due to temporary suppression of pain symptoms. The increased risk of endometriosis observed among past OC users may reflect, at least in part, a true risk due to the higher number of menstrual cycles in OC users [15].

*Weight and peripheral body fat distribution*

A recent review of the literature [16] identified 11 studies on the association between endometriosis and body mass index (BMI) in the adult population. A modest inverse relationship was found between endometriosis and adult BMI. This association may be explained by potential bias. Diagnosis of endometriosis may be more difficult in overweight women. Other potential explanations for this association include the inverse relationship between body weight and socio-economic status, the common phenomenon of weight gain with childbearing, the loss of appetite as a result of disease, more irregular menstrual cycles and increased rates of anovulatory infertility [4,5,17]. A cohort study suggested a persistent inverse relationship between childhood body size and the risk of endometriosis [18], giving some support to the hypothesis that body weight may be 'aetiologically' related to the risk of endometriosis.

*Pigmentary traits and sun habits*

There are some intriguing data supporting a possible association between endometriosis and pigmentary traits or sun habits. A link between endometriosis and melanoma [19] has been suggested. Moreover, the presence of specific phenotypic traits, such as red hair, naevi, freckles and sensitivity to sun exposure,

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