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Perimenopausal management of ovarian endometriosis and associated cancer risk: When is medical or surgical treatment indicated?

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A B S T R A C T

In women with endometriosis, the lifetime risk of ovarian cancer is increased from 1.4% to about 1.9%. The risk of clear cell and endometrioid ovarian cancer is, respectively, tripled and doubled. Atypical endometriosis, observed in 1–3% of endometriomas excised in premenopausal women, is the intermediate precursor lesion linking typical endometriosis and clear cell/endometrioid tumors. Prolonged oral contraceptive use is associated with a major reduction in ovarian cancer risk among women with endometriosis. Surveillance ± progestogen treatment or surgery should be discussed in perimenopausal women with small, typical endometriomas. In most perimenopausal women with a history of endometriosis but without endometriomas, surveillance instead of risk-reducing bilateral salpingo-oophorectomy seems advisable.

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Risk-reducing salpingo-oophorectomy might benefit patients at particularly increased risk, but the evidence is inconclusive. Risk profiling models and decision aids may assist patients in their choice. Screening of the general perimenopausal population to detect asymptomatic endometriomas is unlikely to reduce disease-specific mortality.

Introduction

Endometriosis is associated with a moderate increase in ovarian cancer risk. According to large population-based studies and meta-analyses of cohort and case-control studies, the overall relative risk varies from 1.4 to 1.8 [1–3]. The risk of ovarian cancer appears particularly elevated among subjects with a long-standing history of untreated ovarian endometriosis [4–9]. The main objectives of this review are (i) to suggest a management plan for perimenopausal patients with ovarian endometriomas and (ii) to clarify whether perimenopausal women with a history of endometriosis but without current endometriomas would benefit from prevention interventions in terms of reduced mortality from endometriosis-associated ovarian cancer (EAOC). To this aim, relevant epidemiological and oncological information has been critically reviewed. In this regard, several excellent articles are available on the pathogenesis and classification of ovarian cancers [10–13].

For the purpose of the present review, some definitions need preliminary clarification.

Perimenopause is defined by the World Health Organization and the North American Menopause Society as a period of 2–8 years preceding menopause and 1 year following final menses [14,15]. The age of 45 years is here considered as the lower limit of the perimenopausal period. Endometriomas are defined as typical or atypical based on published ultrasonographic characteristics [16–18]. In the absence of a precise measure consistently indicated by international gynecological and radiological societies, endometriomas are considered as small or large based on the maximum cut-off diameter of 5 cm suggested by Muzii et al. [19]. In addition, the association between endometriosis and specific epithelial ovarian cancer histotypes is assumed to be causal. This view is supported by a large body of evidence and shared by most, albeit not all, authoritative experts in the field [1–3,10–13].

Epidemiological and histopathological outline of the association between endometriosis and ovarian cancer

A woman's lifetime risk of developing ovarian cancer is about 1 in 75 [13]. In western countries, ≥90% of ovarian malignancies are epithelial in origin. According to the dualistic pathogenic model [11], the main epithelial ovarian cancer histotypes are classified as types I and II. The former group comprises the so-called endometriosis-associated tumors that include endometrioid, clear cell, and seromucinous carcinomas. Type II tumors are mainly composed of high-grade serous carcinomas (HGSOC), which represent almost 70% of ovarian carcinomas [11]. Among the EAOC, the seromucinous histotype is fairly rare. Thus, the endometrioid ovarian carcinomas (ENOC) and the clear cell ovarian carcinomas (CCOC) are the most frequent histotypes associated with endometriosis. In particular, it has been suggested that ENOC derive from cells of the secretory cell lineage, whereas CCOC derive from, or have similarities to, cells of the ciliated cell lineage [20].

Women with endometriosis are at about tripled risk for CCOC and doubled risk for ENOC [1]. The prevalence of CCOC is variable, depending on the geographic area considered. In fact, figures between 1% and 13% have been reported in Europe and North America, and between 15% and 25% in some Asian region, particularly in Japan [21]. The prevalence of ENOC varies between 7% and 13% in surgical series. A synchronous carcinoma of the eutopic endometrium has been reported in 15%–20% of cases of ENOC, thus suggesting a common origin or common risk factors [22]. Overall, CCOC and ENOC are, respectively, the second and third most common ovarian cancer histotypes. They represent about 20% of all

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