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

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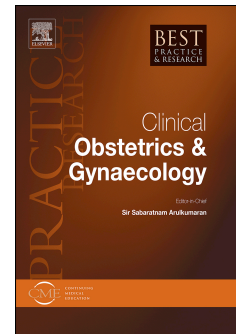
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1 PERIMENOPAUSAL MANAGEMENT OF OVARIAN ENDOMETRIOSIS AND RELATED
2 CANCER RISK: WHEN IS MEDICAL OR SURGICAL TREATMENT INDICATED?

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26

27 ABSTRACT

28

29 In women with endometriosis the lifetime risk of ovarian cancer is increased from 1.4% to about
30 1.9%. The risk of clear cell and endometrioid ovarian cancer is, respectively, tripled and doubled.
31 Atypical endometriosis, observed in 1-3% of endometriomas excised in premenopausal women, is
32 the intermediate precursor lesion linking typical endometriosis and clear cell/endometrioid tumors.
33 Prolonged oral contraceptive use is associated with a major reduction in ovarian cancer risk among
34 women with endometriosis. Surveillance \pm progestogen treatment or surgery should be discussed in
35 perimenopausal women with small, typical endometriomas. In most perimenopausal women with a
36 history of endometriosis but without endometriomas, surveillance instead of risk-reducing bilateral
37 salpingo-oophorectomy seems advisable. Risk-reducing salpingo-oophorectomy might benefit
38 patients at particularly increased risk, but the evidence is inconclusive. Risk profiling models and
39 decision aids may assist patients in their choice. Screening of the general perimenopausal
40 population to detect asymptomatic endometriomas is unlikely to reduce disease-specific mortality.

41

42

43 KEYWORDS

44 Endometriosis; ovarian cancer; risk-reducing salpingo-oophorectomy; endometrioma; medical
45 treatment; screening; early diagnosis.

46

47 1. INTRODUCTION

48
49 Endometriosis is associated with a moderate increase in ovarian cancer risk. According to large
50 population-based studies and meta-analyses of cohort and case-control studies, the overall relative
51 risk varies from 1.4 to 1.8 [1-3]. The risk of ovarian cancer appears particularly elevated among
52 subjects with a long-standing history of untreated ovarian endometriosis [4-9]. The main objectives
53 of this review are i) to suggest a management plan for perimenopausal patients with ovarian
54 endometriomas, and ii) to clarify whether perimenopausal women with a history of endometriosis
55 but without current endometriomas would benefit from prevention interventions in terms of reduced
56 mortality from endometriosis-associated ovarian cancer (EAOC). To this aim, relevant
57 epidemiological and oncological information has been critically reviewed. In this regard, several
58 excellent articles are available on the pathogenesis and classification of ovarian cancers [10-13].

59 For the purpose of the present review, some definitions need preliminary clarification.
60 Perimenopause is defined by the World Health Organization and the North American Menopause
61 Society as the two to eight years preceding menopause and one year following final menses [14,15].
62 The age of 45 years is here considered as the lower limit of the perimenopausal period.
63 Endometriomas are defined as typical or atypical based on published ultrasonographic
64 characteristics [16-18]. In the absence of a precise measure consistently indicated by international
65 gynecological and radiological societies, endometriomas are considered as small or large based on
66 the maximum cut-off diameter of 5 cm suggested by Muzii *et al.* [19]. In addition, the association
67 between endometriosis and specific epithelial ovarian cancer histotypes is assumed to be causal.
68 This view is supported by a large body of evidence and shared by most, albeit not all, authoritative
69 experts in the field [1-3, 10-13].

70

71 2. EPIDEMIOLOGICAL AND HISTOPATHOLOGICAL OUTLINE OF THE ASSOCIATION
72 BETWEEN ENDOMETRIOSIS AND OVARIAN CANCER

73 A woman's lifetime risk of developing ovarian cancer is about 1 in 75 [13]. In western countries \geq
74 90% of ovarian malignancies are epithelial in origin. According to the dualistic pathogenic model
75 [11], the main epithelial ovarian cancer histotypes are classified as type I and II. The former group
76 comprises the so-called endometriosis-associated tumors that include endometrioid, clear cell, and
77 seromucinous carcinomas. Type II tumors are mainly composed of high-grade serous carcinomas
78 (HGSOC), which represent almost 70% of ovarian carcinomas [11]. Among the EAOC, the
79 seromucinous histotype is fairly rare. Thus, the endometrioid ovarian carcinomas (ENOC) and the
80 clear cell ovarian carcinomas (CCOC) are the most frequent histotypes associated with
81 endometriosis. In particular, it has been suggested that ENOC derive from cells of the secretory cell
82 lineage, whereas CCOC derive from, or have similarities to, cells of the ciliated cell lineage [20].

83 Women with endometriosis are at about tripled risk for CCOC and doubled risk for ENOC
84 [1]. The prevalence of CCOC is variable, depending on the geographic area considered. In fact,
85 figures between 1% and 13% have been reported in Europe and North America, and between 15%
86 and 25% in some Asian region, particularly in Japan [21]. The prevalence of ENOC varies between
87 7% and 13% in surgical series. A synchronous carcinoma of the eutopic endometrium has been
88 reported in 15% to 20% of cases of ENOC, thus suggesting a common origin or common risk
89 factors [22]. Overall, CCOC and ENOC are, respectively, the second and third most common
90 ovarian cancer histotypes. They represent about 20% of all ovarian carcinomas, but account for no
91 more than 10% of the deaths from this disease, whereas HGSOC accounts for about 90% of the
92 deaths [11,13,22]. This seems partly due to the fact that most CCOC and ENOC are detected at
93 early stages, when the 5-year survival rate is around 90%, whereas HGSOC are usually detected at
94 advanced stages, with a 5-year survival rate of about 30% [23,24].

95 This striking difference in stage at detection between EAOC and HGSOC seems to be
96 related to different biological behaviors, but also to different pathogeneses and the fact that a
97 precursor lesion is identifiable for CCOC and ENOC, but not for HGSOC. In fact, according to the
98 dualistic model, most HGSOC derives from minute and undetectable atypical lesions within the

99 fimbriated end of the fallopian tube (serous tubal intraepithelial carcinomas, STIC) [25]. When
100 malignant cells exfoliate from STIC, they implant not only on the ovaries, but also on the
101 peritoneum, the omentum, and on abdominopelvic organs. Therefore, most HGSOC develop as late
102 stage cancers from inception. Conversely, most CCOC and ENOC would arise within ovarian
103 endometriotic cysts that are detectable at transvaginal ultrasonography (TVUS), and are confined to
104 the ovary for a variable period of time [11]. Thus, when only one ovary is involved and surgery is
105 promptly undertaken, the disease is usually at stage I.

106 Based on the lifetime risk of developing ovarian cancer in western countries, i.e., 1/75
107 (1.33%), the magnitude of the potential effect of untreated ovarian endometriotic cysts can be
108 tentatively calculated. Considering a prevalence of HGSOC, CCOC, ENOC and “other” histotypes
109 of, respectively, 70%, 10%, 10%, and 10% among ovarian cancers arising in the general female
110 population [13,22], and hypothesizing that the relative risk of developing CCOCs, ENOCs and
111 “other” histotypes is, respectively, 3, 2, and 1.5 in women with endometriosis, the lifetime risk of
112 developing an ovarian cancer in this latter sub-population would be 1/56 (1.79%; difference with
113 the general female population = +0.46%). This is in line with literature findings [1-3].
114 Hypothesizing an overall percent survival for HSGOC, CCOC, ENOC and “other” histotypes of,
115 respectively, 20%, 35%, 55%, and 35%, yields a rough lifetime risk of dying from ovarian cancer of
116 1/100 (1%) in the general female population [13], and of 1/77 (1.31%) in postmenopausal women
117 with untreated ovarian endometriosis (difference with the general female population = +0.31%).
118 These estimates may vary according to the geographical area considered. They are herein calculated
119 only to provide an approximation of the potential epidemiological burden.

120

121 3. MOLECULAR AND GENETIC OUTLINE OF ENDOMETRIOSIS-ASSOCIATED

122 OVARIAN CANCER

123 Molecular pattern of endometriosis-associated ovarian cancers

124 It is puzzling how endometriosis can be the precursor tissue of two distinct ovarian cancer
125 histotypes without any recurrent genetic mutation that is unique to either of them (Table 1). The
126 differences in the genomic landscape features between ENOC and CCOC are not absolute. Thus,
127 mutations alone cannot explain their clinical and phenotypic distinctions and the ovarian
128 environment is likely to play a critical role [20].

129 Ovarian cancer is considered as a hormone-responsive cancer [26]. However, one of the
130 predominant and clinical relevant aspect distinguishing these two histotypes is the differential
131 estrogen receptor expression. The progesterone receptor and estrogen receptor (ER) mediate some
132 effects of female steroid hormones on proliferation and apoptosis of ovarian cancer cells. Actions of
133 estradiol are mediated by two isoforms of ERs: ER α and ER β that differ not only in their tissue
134 distribution, but also in their ligand binding specificity and affinity [26]. Besides subtypes, the
135 presence of ER β variants (β 1- β 5) due to alternative splicing, further complicates the biological
136 significance of ER β signaling. ER β 1 is the only isoform capable of binding ligands while ER β 2 and
137 ER β 5 can heterodimerize with ER β 1 and induce its transcriptional activity ligand-dependently [27].
138 Cytoplasmic ERs are also known to exert effects through nongenomic signaling [26,27]. ER α has
139 been shown to represent an independent prognostic marker for ENOC [28] while nuclear ER α was
140 barely detectable in CCOC. Significant loss of cER β 2 and of cER β 5 expression was also observed
141 in CCOC (Table 1). An improved survival in patients with hormone-receptor-positive tumors has
142 been reported, partly explained by increased numbers of patients who respond to endocrine
143 treatments [28].

144 Although some mutations are present in both histotypes, there are however important
145 molecular differences between CCOC and ENOC:

146 Inactivating ARID1A mutations are the most common molecular genetic alteration reported
147 thus far in CCOC and ENOC, but a higher frequency of ARID1A mutations has been detected in
148 CCOC (46–57%) compared with ENOC (30%) [29]. These mutations result in loss of expression of
149 the protein encoded by ARID1A (BAF250a) which normally suppresses cellular proliferation

150 through a p53-dependent transcription regulation of several tumor suppressors including CDKN1A
151 (encoding p21) and SMAD3 [30]. As a matter of fact, loss of protein expression of the ARID1A
152 tumor suppressor gene has been demonstrated in endometriosis adjacent to clear cell tumor samples
153 [31]. According to Yamamoto and coworkers, ARID1A protein immunoreactivity was deficient in
154 17 (61%) of the 28 CCOC [32]. According to Ayhan *et al.*, loss of ARID1A staining was observed
155 in 75% of the 24 CCOC adjacent to endometriomas [33]. Stamp *et al.* found that the incidence of
156 BAF250a loss was 55% in CCOC and 33% in ENOC [34]. Interestingly, mutations in ARID1A or
157 loss of BAF250a expression have not been shown to be associated with a different cancer
158 phenotype or prognosis in EAO. No differences in the clinical behavior were observed comparing
159 BAF250a-positive versus BAF250a-negative cancers supporting the idea that ARID1A mutations
160 might represent a marker of genomic instability without driving the phenotype [35].

161 Overexpression of the transcription factor HNF-1beta and PIK3CA mutations are also
162 common in CCOC [34,35]. Using whole-genome shotgun sequencing of 7 CCOC and targeted
163 sequencing in synchronous endometriosis, 98% of somatic mutations were found in common
164 between carcinomas and endometriotic lesions. ARID1A and PIK3CA mutations appeared
165 consistently in concurrent endometriosis when present in the primary CCOC [24,36]. Importantly,
166 aberrant expression of ARID1A, PIK3CA, and NF-kB genes has been recognized as the major
167 target genes involved in oxidative stress-induced carcinogenesis and, in the context of the malignant
168 transformation of endometriosis, the high oxidative potential of iron has been emphasized [34].

169 Menstrual red blood cells in the extravascular space tend to lyse quickly and, as a result of
170 hemoglobin oxidization, heme is released. Free heme promotes oxidative damage and formation of
171 reactive oxygen species (ROS), which, in turn, split the heme ring and release redoxactive free iron.
172 Free iron is a strong oxidant and, when present at high levels, contributes to the production of ROS
173 [37-41]. A fine-tuned regulation of lethal and sublethal oxidative stress responses might modulate
174 either cell death or tumor initiation, respectively, due to the iron-induced DNA damage, mutations,
175 and genomic instability. Under the proliferative stress generated by iron and oxidative stress,

176 endometriotic cells can escape apoptosis under the up-regulation of the transcription factor HNF-
177 1beta expression and subsequently re-enter the cell cycle with genotoxic stress. Mutations in
178 ARID1A gene and subsequent protein alteration may result in a defective repair or replication of
179 damaged DNA. Activating mutations of the PIK3CA gene lead to activation of the AKT pathway
180 resulting in improved cancer cell growth, survival and invasion [34]. AKT phosphorylation is also
181 associated with ARID1A/BAF250a deficient tumors [35]. In line with this hypothesis and with the
182 reduction of the hormone dependency of CCOC, oxidative stress has been shown to act as a
183 physiological regulator of ERs [34].

184 A more complex scenario may be foreseen for ENOC based on recent molecular,
185 epidemiologic and histopathologic studies [42]. Endometrioid ovarian cancers possess different
186 clinical characteristics when compared to cancers that are not associated with the disease. Patients
187 with ENOC are younger and are more likely to have low grade and early-stage tumors which are
188 more frequently synchronous to endometrial carcinomas. The fact that synchronous endometrial
189 and ovarian tumors are no longer considered the result of two independently occurring,
190 simultaneous tumors, but are rather clonally derived, opens a new scenario on the origin and/or
191 spread of endometriosis-associated tumors. Site of origin and directionality of metastasis, as well as
192 the specific ovarian and endometrial microenvironment features that may influence progression are
193 however yet to be clarified [43].

194 Major genetic alterations involved in ENOC are represented by PTEN, ARID1A, KRAS and
195 CTNNB1 gene mutations [42]. Mutations in exon 3 of the gene encoding β -catenin (CTNNB1)
196 were identified in 21 (60%) of 35 ENOC, but were not identified in any of the 28 CCOC
197 investigated by Matsumoto and coworkers [44]. Mutations in PTEN gene were identified in 20% of
198 ENOC and in 8.3% of CCOC [45]. KRAS mutations were identified in 12 (29%) of 42 ENOC [46].
199 Mutations in the KRAS gene lead to constitutive activation of the KRAS-BRAF-MEK-MAPK
200 signaling pathway and the resulting sustained MAPK activity has myriad effects on cell function,
201 including cellular proliferation, apoptosis, adhesion and migratory capacity.

202 Cancer driver mutations in endometriosis

203 The transformation of a normal cell into a cancer cell is due to the progressive acquisition of driver
204 mutations. Several studies have evaluated somatic cancer-associated mutations in endometriotic
205 lesions without concurrent cancer in order to assess whether endometriosis might be considered as a
206 precursor of cancer [45]. While TP53 mutations are absent in solitary ovarian endometriotic cysts
207 [45], PTEN mutations were found in 20% and 53% of these lesions in two different studies [47,48].
208 Loss of ARID1A/BAF250a has been observed quite rarely in non-atypical endometriosis (from 0 to
209 20% of samples) while atypical endometriosis was found to be ARID1A/BAF250a negative in a
210 variable proportion of cases according to different studies (from 10% to 100%) [23,34,49]. No
211 PIK3CA mutations were observed in 23 endometriotic samples [23]. Interestingly, KRAS and
212 ARID1A mutations have been recently detected in deep infiltrating endometriotic lesions that very
213 rarely undergo malignant transformation [50]. This poses some doubts on the real oncogenic
214 potential of these mutations. As correctly pointed out by Chui and co-workers, the role of cancer
215 driver mutations has still to be elucidated as well as the correlation between the genotype and the
216 clinical outcomes [51].

217

218 4. IS OVARIAN ENDOMETRIOSIS A PREMALIGNANT LESION?

219 As the lifetime risk of developing an adenocarcinoma of the endometrium is about 2% in the
220 general female population, there seems to be no reason to believe that the same type of mucosa
221 should not undergo malignant derailments at a similar rate when displaced at ectopic sites. Indeed,
222 EAO have been described as endometrial cancers in the wrong place [12]. The chronic
223 inflammatory pelvic environment of women with endometriosis may theoretically even facilitate
224 the transformation of a normal endometrial cell into a malignant cell. However, determining
225 whether the mere presence of endometrium at ectopic sites should be considered *per se* a
226 premalignant condition seems crucial and constitutes the conceptual base of any strategy aimed at
227 reducing EAO mortality. Lesions are defined “precancerous” based on definite epidemiologic,

228 morphologic, molecular, and biologic criteria that imply the acquisition of genetic, karyotypic,
229 structural, or functional changes in a cluster of cells that differentiate them from the surrounding
230 normal tissue [52]. In other words, premalignant lesions should reflect an intermediate stage along
231 the pathway leading to cancer. When enough genetic changes have occurred, modifications in
232 appearance and function are observed, but not yet associated with the typical malignant behavior.
233 Examples includes actinic keratosis, Barrett's esophagus, atrophic gastritis, ductal carcinoma in situ,
234 and cervical dysplasia [52].

235 In 2004 the National Cancer Institute and The George Washington University Cancer
236 Institute convened a conference of expert pathologists with the objective of reaching a consensus on
237 the definition of precancerous lesions. Based on the premise that the identification and elimination
238 of specific cancer precursors would lead to the near-eradication of that type of cancer, it was agreed
239 that the detection of premalignant lesions should not necessarily be based exclusively on histologic
240 criteria. In order to demonstrate the effect of any prevention intervention, it is crucial to
241 appropriately define a precancer independently of detection methods adopted. The five developed
242 defining criteria that must be applied to precancerous lesions are reported in Table 2. According to
243 the authors of the consensus document, *“these five criteria represent the minimal set of conditions
244 for a lesion detected by any method to be considered a precancer. These conditions are necessary
245 and sufficient. All of the criteria must apply, and they all must apply concurrently (i.e. not additive
246 over time)”* [52]. One of the novelties here is that the definition of precancer lesions is not entirely
247 based on specific morphologic features, but also on cytogenetic, molecular, and even behavioral
248 (phenotypic) characteristics.

249 Although all the criteria must simultaneously apply, the third and the fifth ones seems
250 particularly relevant for the endometriosis population. According to the third criterion, a
251 precancerous lesion must be different from the normal tissue from which it arises. In other words,
252 the “normal”, although displaced, endometrium cannot be considered a precancerous lesion. If
253 intrauterine endometrium is the source of the ectopic mucosa, then the usual intermediate steps

254 leading to endometrial cancer (atypical hyperplasia; endometrial intraepithelial neoplasia) should be
255 expected to occur also when the endometrium is located in the pelvis before an “ovarian” cancer
256 develops. Distinguishing premalignant lesions from normal endometrial tissue, malignant tissue,
257 and other lesions is important. As an example, in ovarian endometriotic cysts it is sometimes
258 cumbersome to discriminate between the true cytological/structural atypia and the benign reactive
259 atypia associated with underlying inflammation (Figure 1) [53,54].

260 Several authors indicate only atypical endometriosis, and not normal endometrium at ectopic
261 sites, as a premalignant lesion. Kommoss and Gilks [55] maintain that the assumed precursor of
262 ENOC and CCOC is atypical endometriosis resulting from ovarian implantation of endometrial
263 tissue after trans-tubal spread. Anglesio and Wilbur [24,54] specifies that cytologically atypical
264 *ovarian endometriosis* (large nuclei that are either hyperchromatic or pale, have an increased
265 nucleus-to-cytoplasm ratio, cellular crowding, stratification, or tufting) should be considered the
266 direct precursor of CCOC and ENOC, as atypical endometriosis has been identified contiguous with
267 these tumor histotypes [56]. Samartzis *et al.* [23] maintain that atypical endometriosis should be
268 considered the histological precursor lesion of CCOC, as common truncating mutations and loss of
269 protein expression of the ARID1A tumor suppressor gene have been demonstrated in these tumors
270 and in contiguous atypical endometriosis. However, as previously mentioned, these mutations can
271 also be found in deep infiltrating endometriosis that, according to Anglesio *et al.* [50], is not a
272 cancer precursor. Indeed, according to the results two systematic literature reviews, only a few
273 cases of carcinomas arising in rectovaginal endometriotic lesions have been reported [57,58].

274 Therefore, a specific role seems to be played by the ovarian microenvironment in increasing
275 the risk of malignant derailment [20]. Karnezis concurs that the ovarian microenvironment seems to
276 be essential for the malignant transformation of endometriosis because many endometriotic lesions
277 are located outside the ovary, including the pelvic peritoneum, but carcinomas at such sites are rare
278 [12]. In this regard, Blanco *et al.* observed that the stroma surrounding ovarian epithelial tumors is
279 activated to elaborate steroid hormones which may stimulate further neoplastic growth [59].

280 Kurman *et al.* [11] defined the eutopic endometrium as the *precursor site of origin* of CCOC
281 and ENOC, endometriosis as the *potential precursor lesion*, and atypical endometriosis as the
282 *immediate precursor lesion*. Karnezis indicates endometriosis as the *tissue of origin* of ENOC and
283 CCOC, endometrial epithelial cells as the *cells of origin*, and endometrioid borderline tumors as the
284 *precursor lesion* [12]. According to these views, ectopic endometrium, similarly to the eutopic
285 counterpart, has the *potential* for malignant derailment, but should not be considered a precancer. In
286 addition, Karnezis [12] categorized endometriosis as “high risk” and “low risk”, based on the
287 presence of atypical endometriosis, intended as an intermediate precursor that links typical
288 endometriosis and ovarian cancers.

289 Therefore, given the current consensus on the very low malignant potential of peritoneal
290 endometriosis, be it “superficial”, as in early disease stages, or “deep”, as in rectovaginal plaques,
291 efforts should be focused on the identification of those ovarian endometriotic cysts that include
292 atypical epithelial lesions.

293 Here the fifth criterion for the definition of premalignant lesions states that there must be a
294 method by which the precancer can be diagnosed. According to the authors, “*this requirement is not*
295 *constrained by the diagnostic method, which today is primarily routine histopathologic examination*
296 *of excisional biopsies. Any single or combinatorial diagnostic modality with sufficient sensitivity*
297 *and specificity that is clinically useful may fulfill this requirement. Functional imaging and*
298 *molecular analysis of biologic samples are examples of emergent technology that might be useful in*
299 *this regard*” [52]. This is an important area of future endometriosis research, as the possibility of
300 identifying those endometriomas that harbor atypical epithelial foci would allow, on one hand
301 timely surgery with prevention of lesion progression, and on the other hand conservative
302 management with reduction of morbidity and cost in the majority of women in whom premalignant
303 lesions can be reliably ruled out.

304

305 5. EARLY DETECTION OF ENDOMETRIOSIS-ASSOCIATED OVARIAN TUMORS

306 An in-depth description of ultrasonographic characteristics of the spectrum of ovarian lesions
307 ranging from the so-called “typical” benign ovarian endometrioma to overtly suspicious masses
308 originating from endometriotic cysts is beyond the scope of the present review, and the reader may
309 refer to several authoritative articles, including those by Exacoustos *et al.* [16] and Guerriero *et al.*
310 [17,18]. Here only summary information is given regarding some elements that may increase the
311 awareness towards a possible malignant derailment of ovarian endometriosis.

312 According to Exacoustos *et al.* [16], the ‘typical’ endometrioma is a unilocular or
313 multilocular (one to four locules) cyst, with homogeneous low-level echogenicity (ground glass
314 echogenicity) of the cyst fluid, no solid parts, and no papillations with detectable blood flow,
315 detected in a premenopausal woman. Papillary projections are protrusion of solid tissue into the cyst
316 lumen with a height of 3 mm or more. The ultrasonographic characteristics of endometriomas may
317 differ according to pre- or postmenopausal status. Endometriotic cysts in postmenopausal women
318 are more frequently multilocular, and less likely to exhibit ground glass echogenicity, as anechoic
319 cyst fluid or cyst fluid with mixed echogenicity is often observed [16]. Guerriero *et al.* confirmed
320 that in older women multilocular cysts and cysts with papillations and other solid components
321 become more common whereas ground glass echogenicity of cyst fluid becomes less common
322 compared with endometriomas observed in younger women. Interestingly, the maximal cyst
323 diameter does not seem to vary significantly with age [18].

324 Nezhat *et al.* warns that an increase in endometrioma size in postmenopause or during
325 hormonal therapy in premenopause, modification of ultrasonographic characteristics, and
326 appearance of mural node formation constitute ominous signs that require surgical excision [10].
327 Relapsing or worsening pelvic pain symptoms, such as newly developed dysmenorrhea and
328 dyspareunia, should further increase the index of suspicion [23]. Advancing age (≥ 45 years) and
329 the size of endometriomas (≥ 8 cm) were independent predictors of development of ovarian cancer
330 among women with ovarian endometrioma [6,7,60].

331 At TVUS, borderline tumors and carcinomas arising from endometriotic cysts generally
332 show a vascularized solid component [16]. Tanase *et al.* [61] reported that, whereas in
333 premenopausal women the majority of mural nodular lesions observed within ovarian
334 endometriomas were retracted blood clots, in older women and those with larger cyst diameters,
335 mural nodules were more likely malignant, especially in case of large nodule sizes and taller than
336 wider lesions. Also in the study by Taniguchi *et al.* [62] the rapid growth of an endometrioma and
337 the presence of mural nodules were the most reliable predictors of malignancy.
338 In the large series of Kuo *et al.* [63], the frequency of unexpected EAO in presumed ovarian
339 endometriomas was 0.14%. All patients with malignancies were aged ≥ 40 years and almost two
340 thirds of them had vegetations within the ovarian cyst at preoperative ultrasonography.

341 Evaluation of all suspicious endometriomas by gynecologists or radiologists with specific
342 oncological experience may greatly increase the performance of imaging techniques in the detection
343 of those cysts that requires prompt surgical removal. In this regard, according to the
344 recommendations of the First International Consensus Report on Adnexal Masses, “*despite*
345 *extensive research into various risk prediction models, subjective assessment in the hands of an*
346 *expert remains as accurate as any technique for assessment of adnexal masses by sonography.*
347 *Thus, it is appropriate to consider referral to an expert gynecologic sonologist when faced with a*
348 *challenging or indeterminate adnexal mass*” [64].

349 Of relevance here, the debate on ultrasonographic signs of malignancy does not shed light
350 on the possibility of identifying premalignant endometriomas, i.e. endometriomas harboring
351 atypical lesions. Ultrasonographic findings may significantly differ between endometriomas
352 degenerated into cancer and endometriomas with atypical lesions. Specific studies aimed at
353 disentangling this issue are currently lacking and represent a research priority. Noteworthy, this
354 kind of studies should rely on vast series of women, as atypical endometriosis is rare, and should be
355 prospectively undertaken in centers systematically performing a thorough and detailed pre-surgical
356 TVUS evaluation following a standardized methodology [18].

357 6. MANAGEMENT OF PERIMENOPAUSAL WOMEN WITH OVARIAN
358 ENDOMETRIOMAS

359 When a typical ovarian endometrioma of < 5 cm is identified in a young woman seeking conception
360 in the future, the risk of iatrogenic ovarian reserve reduction may suggest refraining from surgery
361 [19]. Moreover, when surgery for endometriomas is chosen in women of < 45 years of age, gonadal
362 conservation may be preferable even when pregnancy desire is no longer an issue, as premature
363 hypo-estrogenism may increase the risk of cardiovascular events and all-cause mortality [65].
364 However, when women approach the menopause, the reproductive and hormonal benefits deriving
365 from surgical abstention or conservative procedures progressively vanish. Therefore, removal of
366 ovaries with endometriotic cysts may be discussed in perimenopausal women.

367 Unfortunately, no robust information is available on the effect of surveillance compared
368 with that of surgery (unilateral salpingo-oophorectomy or cystectomy/partial ovarian excision) on
369 mortality from EAO in patients with endometriosis/endometriomas. According to the results of a
370 case-control study conducted by Rossing *et al.* [8], the risk of invasive epithelial ovarian cancer
371 varied according to performance of ovarian surgery after the diagnosis of endometriosis. In fact,
372 with respect to women without a history of endometriosis, the OR of ovarian cancer was 1.6 (95%
373 CI: 1.1–2.3) among women with endometriosis who did not undergo surgery, and 1.2 (95% CI: 0.5–
374 2.5) among those who did. Moreover, only unilateral salpingo-oophorectomy appeared protective
375 (OR, 0.8; 95% CI: 0.3–2.1), whereas cystectomy/partial ovarian excision was not (OR, 3.3; 95% CI:
376 0.7–15.3). In particular, the OR of ENOC and CCOC was 3.2 (95% CI: 1.9–5.6) among women
377 with a history of endometriosis with no subsequent ovarian surgery, compared with 1.6 (95% CI:
378 0.4–5.7) among those who underwent ovarian surgery. However, the small number of cases limited
379 the precision of the estimates. In fact, only 94 women with a history of endometriosis were included
380 in this study, and only 20 of them underwent previous ovarian surgery.

381 In the nested case-control study by Melin *et al.* [9], all women with a first-time discharge
382 diagnosis of endometriosis in the period 1969–2007 were identified using the National Swedish

383 Patient Register, and all women diagnosed with epithelial ovarian cancer at least one year after the
384 endometriosis diagnosis (cases) were identified by linkage to the National Swedish Cancer Register.
385 Matched controls were randomly selected from the study base. A significant association was
386 observed between unilateral salpingo-oophorectomy, as well as radical excision of all visible
387 endometriosis, and ovarian cancer risk (adjusted OR, 0.19; 95% CI 0.08–0.46 and 0.30; 95% CI
388 0.12–0.74, respectively). Unfortunately, no information has been provided on ovarian cancer
389 histotype, thus the effect of unilateral salpingo-oophorectomy is expected. Moreover, the
390 categorization of radical versus non-radical endometriosis excision was based on retrospective
391 review of surgical notes.

392 In case unilateral salpingo-oophorectomy is performed, the risk of overall ovarian cancer
393 mortality is reduced by definition, but this effect may be largely due to a decrease in the risk of
394 death from HGSOE following salpingectomy, rather than from CCOC and ENOC following
395 removal of ovaries with endometriomas. Therefore, the results of the above two studies do not
396 definitively clarify whether surgery specifically aimed at removing ovaries with endometriomas is
397 better than surveillance, in terms of reduced mortality from EAOC, for perimenopausal
398 endometriosis patients.

399 Consequently, two different clinical approaches may be envisaged in perimenopausal
400 women with small (< 5 cm), typical endometriomas, i.e., i) removal of the affected ovary/ovaries
401 plus bilateral salpingectomy, especially in cases of long-standing endometriomas in women who are
402 not using OC or progestogens, or ii) strict surveillance ± progestogen treatment with immediate
403 surgery in case of modifications of ultrasonographic cyst patterns (e.g., cyst volume increase and
404 appearance of septa, papillary projections, mural nodules, or changes in vascularization), or
405 suspicious rise in serum CA 125 and human epididymis protein 4 (HE4) levels. In theory,
406 surveillance could be justified by the fact that endometriosis-related cancers usually remain intra-
407 cystic for a variable period of time [11,22].

408 The median age at diagnosis of ENOC and CCOC is, respectively, 47 and 55 years
409 [21,22,23]. Therefore, the effect size of surgery is likely directly related with the age at which the
410 affected ovaries are removed. Surgery should be considered in case of long-standing
411 endometriomas [4-7], especially if they are not being treated with oral contraceptives (OC) or
412 progestogens, but also in case of de-novo detection of an endometrioma during medical treatment,
413 as the risk of malignancy appears here substantially increased [7,61,63]. Moreover, according to
414 Haraguchi *et al.* [66] recurrent endometriomas are at especially augmented risk of malignant
415 transformation, as all EAOE in their series developed in patients who experienced a cyst
416 recurrence.

417 Not removing the ovary with endometriotic cysts means that perimenopausal women should
418 undergo periodic TVUS and serum marker level measurements for many years. In addition, the
419 variable degree of anxiety caused by knowing of being at increased risk for a dreadful cancer
420 should be carefully weighed. These factors augment the overall burden of treatment, including out-
421 of-pocket costs, and may unfavorably impact on health-related quality of life [67]. On the other
422 hand, the patient medical history must be considered because, especially when multiple and
423 extensive abdominopelvic procedures have been performed, the operative risk may be increased to
424 the point that sometimes the balance may be tipped toward expectant management. Removing the
425 adnexa when previous surgical notes report the presence of extensive and dense pelvic adhesions
426 with difficult visualization of the internal genitalia (frozen pelvis), exposes to an increased risk of
427 bowel and ureteral lesions, as well as of the ovarian remnant syndrome [68]. In case surgical
428 abstention is chosen, progestogens may be used as a therapeutic measure during surveillance, after
429 information is provided on the potential benefits and potential harms of combining periodic
430 assessments with medical therapy in specific clinical conditions. Regrettably, insufficient data are
431 available on variation of EAOE risk when hormonal treatments are started during perimenopause.
432 Suspicious modifications of TVUS appearance or increase in cyst size during suppressive medical
433 therapy requires prompt surgical exploration.

434 A further aspect to be discussed with the perimenopausal patient with deep lesions in
435 addition to ovarian endometriomas is whether, in case bilateral salpingo-oophorectomy is decided,
436 deep lesions should also be removed. Symptoms must guide the choice, as only persistent pain
437 despite hypo-estrogenizing medical treatment justifies the additional surgical risk of excising
438 lesions that very rarely undergo malignant transformation and that will most likely become
439 quiescent after gonadal removal. In case the ovaries are removed, but deep lesions are left in place,
440 tibolone or combinations including a progestogen should be used in women requesting hormone
441 replacement therapy [69].

442 All the above information should be provided to perimenopausal patients with
443 endometriomas, and uncertainties should be openly discussed. No robust evidence seems to exist to
444 support either surveillance or surgery in all women with small, typical endometriomas. A
445 commonsense approach may be adopted in these circumstances, that is, suggesting surveillance in
446 patients at high surgical risk, and surgery in those at average surgical risk. If surveillance is chosen
447 in women not using medical therapies, the possibility of starting treatment with progestogens
448 should be discussed. Surgery is obviously the only reasonable choice when large and/or doubtful
449 endometriomas are present.

450

451 7. RISK-REDUCING MEDICAL TREATMENT IN PERIMENOPAUSAL WOMEN

452 Prolonged OC use is associated with a major reduction in the risk of developing an endometrioma
453 [70,71]. This effect seems to be due to ovulation inhibition, as endometriomas have been
454 demonstrated to derive from corpora lutea [72]. Therefore, OC and progestogens should
455 theoretically reduce the risk of both, ENOC and CCOC in women with a history of endometriosis,
456 but without current endometriomas. This risk-reducing effect seems an important added value of
457 OC and progestogens in symptomatic endometriosis patients, even in the late reproductive years.

458 Moreover, according to Kim [2], the carcinogenic process leading to ENOC is primarily an
459 estrogen-rich, progesterone-poor hormonal environment, whereas persistent oxidative stress

460 induced by a high intra-cystic level of heme and free iron may result in stress-resistant type such as
461 CCOC. Thus, in theory, OC and progestogens use for prolonged periods of time in women who
462 already have endometriomas may reduce the risk of mainly receptor-positive ENOC to a greater
463 extent with respect to the risk of mainly receptor-negative CCOC. However, there are currently no
464 data to support this hypothesis.

465 Modugno *et al.* [73], after pooling data from four population-based case-control studies on
466 epithelial ovarian cancer comprising 2098 cases and 2953 control subjects, observed that use of
467 OCs for >10 years was associated with a major reduction in ovarian cancer risk among women with
468 endometriosis (odds ratio, 0.21; 95% CI, 0.08-0.58). Unfortunately, information on the effect of OC
469 specifically on EAOC was not available. Actually, it seems difficult to define differences in the
470 effect of OC on various ovarian cancer histotypes, and it may not be excluded that the results were
471 largely due to a reduction in risk of HGSOC, similarly to what has been observed in the general
472 population [74,75].

473 Independently of histotypes, the reduction in ovarian cancer risk in endometriosis patients
474 refers to OC use *before* menopause. In premenopausal women with a history of endometriosis and
475 without current endometriomas, prolonged OC and progestogen use should be suggested until the
476 natural menopause is reached, as the reduction in risk is directly related with duration of use. In
477 addition, this protective effect extends for decades after OC use are discontinued [74,76]. In the
478 model developed by Pearce *et al.* [76], OC use was essentially absent among the women at higher
479 (> 4%) lifetime ovarian cancer risk (2015). There is no rationale supporting the use of hormonal
480 treatments *after* menopause, neither as a preventive nor as a therapeutic measure.

481

482 8. SURVEILLANCE OR RISK-REDUCING SURGICAL TREATMENT IN 483 PERIMENOPAUSAL WOMEN WITH A HISTORY OF ENDOMETRIOSIS BUT WITHOUT 484 ENDOMETRIOMAS?

485 i) Surveillance

486 The potential benefits of surveillance of the population of asymptomatic women with a previous
487 diagnosis of endometriosis but without endometriomas are currently unknown. It is not possible to
488 exclude that periodic assessment in a population at higher risk according to risk profiling models
489 similar to that developed by Pearce *et al.* [76] may result in a reduction in mortality from ENOC
490 and CCOC, also considering the different pathogenesis and natural history with respect to HGSOC.
491 In fact, STIC, the precursor lesion of HGSOC, is so small that TVUS cannot detect it. The situation
492 is different for EAOC, because they usually develop from epithelial atypia within ovarian
493 endometriomas and are initially confined to one ovary. Therefore, in the case of ENOC and CCOC,
494 detecting a de-novo ovarian cyst with TVUS characteristics of an endometrioma in women at
495 increased risk, may allow timely surgery with eradication of stage I disease (or suspicious cysts
496 without overt carcinomas) without extra-ovarian dissemination and with good long-term prognosis.
497 However, given that type I tumors account for only 10% of the deaths from ovarian cancer, it is
498 unclear if a prevention strategy aimed at identifying early EAOC would impact on the overall
499 mortality from ovarian cancer.

500 The conceptual premise for such a surveillance program in premenopausal endometriosis
501 patients, is that all women with newly detected endometriomas after the age of 45 years should
502 undergo removal of the affected ovary and, when there is no pregnancy desire, also of both
503 fallopian tubes. This would reduce not only the risk of EAOC, but also of HGSOC, thus increasing
504 the benefit of periodic assessment.

505 ii) Risk-reducing surgical treatment

506 With “risk-reducing surgical treatment” we here refer to a patient population with a previous
507 diagnosis of endometriosis/endometriomas, but with no current evidence of endometriotic ovarian
508 cysts, and the question to be answered is whether women with a history of endometriosis but
509 without ovarian endometriomas at TVUS should undergo prophylactic salpingo-oophorectomy
510 when approaching the natural menopause.

511 In the risk profiling model developed by Pearce *et al.* [76], five risk and protective factors
512 were taken into account (i.e., OC use, parity, tubal ligation, endometriosis, and first-degree family
513 history of ovarian cancer in conjunction with a genetic risk score) to define the distribution of
514 lifetime ovarian cancer risk in the general population of up to age 85 for non-Hispanic white
515 women. Risk/protective factor profiles were developed combining the distribution of these variable,
516 considering the relative risks derived from published data, and using control data derived from four
517 representative population-based U.S. studies. The estimated lifetime ovarian cancer risk for 214
518 combinations of risk/protective factors ranged from 0.35% (95% CI, 0.29–0.42) to 8.78% (95% CI,
519 7.10–10.9). In the higher quintile genetic risk scores, most women with lifetime risk ranging from
520 4% to 8% had a self-reported history of endometriosis. As an example, nulliparous endometriosis
521 patients with a negative family history for ovarian cancer and who did not undergo tubal ligation,
522 have a lifetime risk of 4.03% (95% CI, 3.29%–4.94%) if they used OC for 1–4 years, and of 4.40%
523 (95% CI, 3.71%–5.20%) in case they did not use OC. Most other reported combinations of factors
524 are associated with even greater lifetime ovarian cancer risks, with point estimates ranging from
525 4.81% to 7.99%. However, in routine practice the background genetic risk of endometriosis patients
526 is usually unknown. Moreover, the frequency of women included in subgroups at higher ovarian
527 cancer risk is very low, ranging from 0.02% to 0.11% of the general population [76] (Pearce 2015).
528 Finally, external validation of the model by Pearce *et al.* [76] is lacking.

529 Manchanda *et al.* [77] conducted a healthcare economy analysis to define risk thresholds at
530 which risk-reducing salpingo-oophorectomy can be cost-effective for the prevention of sporadic
531 ovarian cancer in lower risk (BRCA negative) women aged 51 years. A decision-analytic model
532 was developed to compare the costs and effects of offering risk-reducing salpingo-oophorectomy
533 for 2%, 4%, 5%, 6%, 8% and 10% lifetime ovarian cancer risk thresholds. At the 2% ovarian cancer
534 risk level, routine risk-reducing salpingo-oophorectomy does not save more quality-adjusted life
535 years (QALY) and is not cost-effective. At a 4% ovarian cancer risk level, risk-reducing salpingo-
536 oophorectomy saves more QALYs but is not cost-effective at the incremental cost-effectiveness

537 ratio = £25,577, which is above the £20,000 U.K. (\$ 26,650; €22,605) National Institute for Health
538 and Care Excellence (NICE) threshold. However, at risk thresholds of $\geq 5\%$, risk-reducing salpingo-
539 oophorectomy saves more life-years and QALYs and is highly cost-effective. According to this
540 model, and based on the lifetime ovarian cancer risk estimates reported by Pearce *et al.* [76], risk-
541 reducing bilateral salpingo-oophorectomy appears cost-effective only in women with endometriosis
542 considered at high risk.

543 In the NICE guideline NG73 a suggestion regarding this specific area of endometriosis
544 management was not deemed opportune because, as an absolute risk is difficult to quantify,
545 *“recommendations would not aid decision making, would cause anxiety in women with*
546 *endometriosis and could be misconstrued, for example women seeking treatments (such as removal*
547 *of the ovaries) that this small risk increase would not warrant”*. Moreover, the Committee also
548 stated *“the potential harms associated with misinterpretation or over-interpretation of any*
549 *recommendation based on this data would outweigh any benefits conferred by women being*
550 *specifically informed about this data. This may lead to unnecessary procedures”* [78, pages 116-
551 118]. The above position refers to women with endometriosis in general, and not to those with
552 current ovarian endometriomas.

553 Overall, no sufficiently robust data are available to justify systematic risk-reducing salpingo-
554 oophorectomy in all women with a previous diagnosis of endometriosis, but without current
555 evidence of endometriomas. Thus, this preventive measure should be discussed only with women at
556 highly increased risk, such as those who report a positive family history of ovarian cancer, of
557 infertility, and who have never used OC.

558 A special situation is when a histologic diagnosis of cytological and/or structural atypia has
559 been made on a previously excised endometrioma, and the ovary has not been removed because of
560 pregnancy desire. Although cystectomy likely eradicated the lesion, persisting predisposing factors
561 may pose that woman at high risk of developing a EAOC, thus it seems prudent to discuss

562 prophylactic bilateral salpingo-oophorectomy after the age of 45 years even if the ovaries are
563 normal at TVUS and serum CA 125 and HE4 levels are not increased [24].

564 According to available studies, atypical endometriosis foci are detected in 1%–3% of
565 ovarian endometriotic cysts [79-81]. However, it is unclear whether those endometriomas were all
566 judged preoperatively as low-risk, or whether also endometriomas with suspicious findings were
567 included. Moreover, frequencies were not reported according to strata of age, and it is not possible
568 to exclude that prevalence rates may be directly related with patient age. In a series of 874
569 endometriomas without suspicious findings at preoperative TVUS removed in 516 patients, the
570 prevalence of true atypical endometriosis was 1.0% (95% CI, 0.5% to 1.9%) based on the number
571 of cysts, and 1.7% (95% CI, 0.9% to 3.3%) based on the number of women [53].

572 An additional problem here is defining the rate of progression of atypical endometriosis
573 toward CCOC and ENOC. In fact, it is accepted that only a fraction of precursor lesions progress
574 toward frank malignancy, and this figure would be important in order to plan effective prevention
575 strategies.

576

577 9. SCREENING FOR ASYMPTOMATIC ENDOMETRIOMAS BETWEEN PREVENTION 578 AND OVERDIAGNOSIS

579 Screening has been defined by the UK National Screening Committee as “*the systematic*
580 *application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to*
581 *warrant further investigation or direct preventive action, amongst persons who have not sought*
582 *medical attention on account of symptoms of that disorder*” [82]. The main objective of screening
583 for ovarian cancer is to decrease the number of deaths from this disease. A secondary aim of
584 screening is to increase the life expectancy of women who develop ovarian cancer [83]. The
585 modality through which screening should decrease mortality is mostly by identifying pre-neoplastic
586 lesions before they become overt ovarian cancer; the modality through which screening should

587 increase life expectancy is by allowing detection of already developed ovarian cancer when it is still
588 confined within the ovary.

589 Thus, given that superficial and deep peritoneal endometriosis very rarely undergo
590 malignant transformation, any screening program aimed at reducing mortality from EAOc should
591 be targeted at detecting endometriotic cysts with atypical lesions, as well as stage I EAOc, in the
592 general population. Unfortunately, screening programs for ovarian cancer have so far been
593 disappointing. Results from the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening
594 trial indicated no mortality benefit and added morbidity due to increased surgical intervention [84].
595 Extended follow-up (median, 14,7 years) of the PLCO trial did not yielded more favorable results
596 from screening for ovarian cancer with CA-125 and TVUS [85]. Recently, even the results of the
597 UK collaborative trial of ovarian cancer screening (UKCTOCS) [86] have been heavily questioned
598 based on methodological and other aspects [83]. Thus, because a reduction in mortality from
599 ovarian cancer as a result of screening has not been documented, it is not routinely offered in the
600 general population *tout court*, independently of ovarian cancer histotypes [77,83]. Indeed, the
601 PLCO and the UKCTOCS screening trials obviously were not limited to the detection of HGSOc
602 and, within the framework of such strategies, all suspicious ovarian lesions, including
603 endometriosis-related tumors, were surgically removed. Despite this, survival has not changed.

604 Beyond good intentions, any screening strategy should translate into a demonstrable
605 reduction in disease-specific mortality, although many epidemiologists would argue that the effect
606 of any screening should be reflected in a reduction of all-cause mortality. Importantly, health
607 economy evaluations should be conducted in order to assess the efficiency of any prevention
608 measure, that is, the effect of an intervention in relation to the resources it consumes (is it worth the
609 effort?), before fostering its implementation into clinical practice.

610 With regard to the possibility of screening for EAOc, the NICE guideline NG73 committee
611 considered “*that there is no national screening available for ovarian cancer and that there is no*

612 *clear management plan that would help to reduce a possible small increased risk* [in women with
613 *endometriosis*]” [78, page 116].

614

615 10. THE CENTRAL ROLE OF INFORMED PATIENTS: HOW TO COMMUNICATE THE 616 RISK

617 Hazel Thornton wrote an enlightening editorial on the practical and ethical implications of different
618 modalities to communicate the benefits, harms, and risks to patients [87]. Physicians must
619 understand statistics and their meaning, know how to access reliable information, and develop the
620 capability of communicating the relevant information in a clear and easily comprehensible manner.
621 Without these premises, patient-centered medicine is simply impracticable. There is no single
622 approach to management of perimenopausal women with small endometriomas, and the pros and
623 cons of surgery and strict surveillance in different clinical conditions should be impartially
624 explained. The temptation for both parties to “do something” and thus chose extirpative surgery is
625 expected, but may not always be the best option in high surgical risk patients at low EAOC risk
626 according to risk profiling models. Uncertainties should be addressed without fear of losing patient
627 trust. Representing evidence as natural frequencies fosters greater insight than percentages or
628 probabilities. Relative risks should never be used as they may convey a distorted information.
629 According to Thornton, worry can be manipulated also by the labelling of outcomes.

630 The most controversial issue is probably risk-reducing salpingo-oophorectomy in the
631 absence of TVUS detected endometriomas. Patient should know that the increase in risk, in
632 absolute terms, is around half of a point percentage of developing an ovarian cancer and a third of a
633 point percentage of dying from ovarian cancer compared with the general female population
634 without a history of endometriosis. In other words, they should be informed that, rounding up, their
635 lifetime probability of *not* developing an ovarian cancer is about 98% instead of 99%. When
636 counseling women, several variables should be discussed, including factors that may impact on the
637 risk of developing EAOC, such as prolonged use of OC or progestogens, parity, and family history.

638 Patients should also be invited to consider the additional surgical risk associated with previous
639 surgical procedures, as well as with individual factors such as severe co-morbidities or obesity.

640 Manchanda *et al.* suggest the development of patient decision aids to facilitate
641 understanding of risk [77]. Specific informed consent forms for different clinical conditions would
642 need to be elaborated as well. According to Pearce *et al.* [76], “*the precise lifetime risk at which a*
643 *woman would consider a risk-reducing salpingo-oophorectomy is a matter to be decided by the*
644 *woman in consultation with her physician. For women who are at, for example, three times the*
645 *average lifetime risk of ovarian cancer (4.11% vs. 1.37%), such a discussion might be warranted*”.

646 However, only a minority of endometriosis patient without endometriomas is at such highly
647 increased risk. Indeed, the NICE Committee maintained “*there needs to be a balance between*
648 *women being fully informed about their condition (including related risks), with rationales for not*
649 *encouraging unnecessary treatments*” [78, page 116].

650

651 SUMMARY

652 The lifetime risk of ovarian cancer is increased from 1.4% in the general population to about 1.9%
653 in women with endometriosis. The risk of clear cell and endometrioid ovarian cancer is,
654 respectively, tripled and doubled in women with endometriosis. These histotypes account for
655 approximately 20% of all ovarian cancer and < 10% of deaths from ovarian cancer. Contrarily to
656 clear cell tumors, endometrioid cancers are generally estrogen sensitive and associated with
657 hormonal risk factors. Clear cell ovarian cancers may be caused by the mutagenic content of
658 endometriomas, rich of free heme- and catalytic iron-derived reactive oxygen species. Atypical
659 endometriosis, observed in 1-3% of endometriomas excised in premenopausal women, is the
660 intermediate precursor lesion that links typical endometriosis and clear cell/endometrioid tumors.
661 Oral contraceptive use for >10 years is associated with about 80% reduction in ovarian cancer risk
662 among women with endometriosis. Surveillance \pm progestogen treatment or surgery should be
663 discussed in perimenopausal women with small typical endometriomas. If surgery is chosen in
664 women not wishing conception, removal of affected ovaries, rather than cystectomy, together with
665 bilateral salpingectomy should be performed, especially in case of long-standing or recurrent
666 endometriomas. In most perimenopausal women with a history of endometriosis but without
667 endometriomas, surveillance instead of risk-reducing bilateral salpingo-oophorectomy seems
668 advisable. Hypothetically, risk-reducing salpingo-oophorectomy may benefit patients at particularly
669 increased risk, but supporting evidence is limited. Risk profiling models and decision aids may
670 assist patients in their choice. Screening of the general population to detect asymptomatic
671 endometriomas is unlikely to reduce disease-specific mortality.

672

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690

691 **Practice Points:**

- 692 • Endometriosis is associated with a three-fold increase in risk of endometrioid and clear-cell
693 ovarian cancer
- 694 • Atypical endometriosis is the precursor lesion of endometriosis-associated ovarian cancers
695 and is observed in 1-3% of ovarian endometriomas removed in premenopausal women
- 696 • The lifetime risk of ovarian cancer in women with a history of endometriosis is about 1.9%
697 compared with 1.4% in the general population
- 698 • Long periods (≥ 10 years) of oral contraceptive use greatly reduce the risk of ovarian cancer
699 in women with a history of endometriosis
- 700 • In most women with a history of endometriosis but without ultrasonographic evidence of
701 endometriomas, surveillance rather than risk-reducing salpingo-oophorectomy seems
702 advisable
- 703 • In women with small, long-standing typical endometriomas, removal of the affected
704 ovary/ovaries and bilateral salpingectomy can be considered when approaching the
705 menopause

707 **Research Agenda:**

- 708 • The potential benefit of risk-reducing salpingo-oophorectomy in women with a history of
709 endometriosis should be better defined according to different risk profiles
- 710 • Potential benefits, potential harms, and healthcare economic aspects of prolonged
711 surveillance in asymptomatic women with a history of endometriosis but without current
712 endometriomas should be assessed in a randomized, controlled trial
- 713 • Early markers of the malignant potential of endometriomas removed at conservative surgery
714 should be identified
- 715 • Surveillance and management strategies for women with a previous histologic diagnosis of
716 atypical endometriomas should be defined

- 717 • Patient decision aids should be developed to facilitate women comprehension of actual risks
718 and support shared decision-making in different clinical conditions

719

ACCEPTED MANUSCRIPT

720 REFERENCES

721

722 [1] Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association

723 between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis

724 of case-control studies. *Lancet Oncol* 2012;13:385-94.*

725 [2] Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with

726 endometriosis: a meta-analysis. *Br J Cancer*. 2014;110:1878-90.

727 [3] Saraswat L, Ayansina D, Cooper KG, Bhattacharya S, Horne AW, Bhattacharya S. Impact of

728 endometriosis on risk of further gynaecological surgery and cancer: a national cohort study. *BJOG*.

729 2017 Sep 27. doi: 10.1111/1471-0528.14793. In press.

730 [4] Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge

731 diagnosis of endometriosis. *Am J Obstet Gynecol*. 1997;176:572-9.

732 [5] Melin A, Sparén P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special

733 emphasis on ovarian cancer. *Hum Reprod*. 2006;21:1237-42.

734 [6] Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, et al. Risk of

735 developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka,

736 Japan. *Int J Gynecol Cancer*. 2007;17:37-43.

737 [7] Kobayashi H, Sumimoto K, Kitanaka T, Yamada Y, Sado T, Sakata M, et al. Ovarian

738 endometrioma--risks factors of ovarian cancer development. *Eur J Obstet Gynecol Reprod Biol*.

739 2008;138:187-93.

740 [8] Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial

741 ovarian cancer in relation to benign ovarian conditions and ovarian surgery. *Cancer Causes Control*.

742 2008;19:1357-64.

- 743 [9] Melin AS, Lundholm C, Malki N, Swahn ML, Sparèn P, Bergqvist A. Hormonal and surgical
744 treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand.*
745 2013;92:546-54.
- 746 [10] Nezhat FR, Apostol R, Nezhat C, Pejovic T. New insights in the pathophysiology of ovarian
747 cancer and implications for screening and prevention. *Am J Obstet Gynecol* 2015;213:262-7.
- 748 **[11] Kurman RJ, Shih IeM. The Dualistic Model of Ovarian Carcinogenesis: Revisited,**
749 **Revised, and Expanded. *Am J Pathol.* 2016;186:733-47.***
- 750 [12] Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian
751 cancers: pathogenesis and prevention strategies. *Nat Rev Cancer.* 2017;17:65-74.
- 752 [13] Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer Biol*
753 *Med.* 2017;14:9-32.
- 754 [14] World Health Organization. Research on the menopause in the 1990's. Report of a WHO
755 Scientific Group. *World Health Organ Tech Rep Ser.* 1996;866,12-14.
- 756 [15] North American Menopause Society. Clinical challenges of perimenopause: consensus opinion
757 of the North American Menopause Society. *Menopause.* 2000;7:5-13.
- 758 **[16] Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and**
759 **adenomyosis. *Best Pract Res Clin Obstet Gynaecol.* 2014;28:655-81.***
- 760 **[17] Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FP, Van Schoubroeck D, et**
761 **al. Systematic approach to sonographic evaluation of the pelvis in women with suspected**
762 **endometriosis, including terms, definitions and measurements: a consensus opinion from the**
763 **International Deep Endometriosis Analysis (IDEA) group. *Ultrasound Obstet Gynecol.***
764 **2016;48:318-32.***

- 765 [18] Guerriero S, Van Calster B, Somigliana E, Ajossa S, Froyman W, De Cock B, et al. Age-
766 related differences in the sonographic characteristics of endometriomas. *Hum Reprod*
767 2016;31:1723-31.
- 768 [19] Muzii L, Tucci CD, Felicianantonio MD, Galati G, Verrelli L, Donato VD, et al. Management of
769 Endometriomas. *Semin Reprod Med* 2017;35:25-30.
- 770 [20] Cochrane DR, Tessier-Cloutier B, Lawrence KM, Nazeran T, Karnezis AN, Salamanca C, et
771 al. Clear cell and endometrioid carcinomas: are their differences attributable to distinct cells of
772 origin? *J Pathol* 2017;243:26-36.
- 773 [21] del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the
774 literature. *Gynecol Oncol.* 2012;126:481-90.
- 775 [22] Prat J. Pathology of borderline and invasive cancers. *Best Pract Res Clin Obstet Gynaecol.*
776 2017;41:15-30.
- 777 **[23] Samartzis EP, Noske A, Dedes KJ, Fink D, Imesch P. ARID1A mutations and PI3K/AKT**
778 **pathway alterations in endometriosis and endometriosis-associated ovarian carcinomas. *Int J***
779 ***Mol Sci.* 2013;14:18824-49.***
- 780 [24] Anglesio MS, Yong PJ. Endometriosis-associated Ovarian Cancers. *Clin Obstet Gynecol*
781 2017;60:711-27.
- 782 [25] Labidi-Galy SI, Papp E, Hallberg D, Niknafs N, Adleff V, Noe M, et al. High grade serous
783 ovarian carcinomas originate in the fallopian tube. *Nat Commun.* 2017;8:1093.
- 784 [26] Chan KKL, Siu MKY, Jiang YX, Wang JJ, Wang Y, Leung THY, et al. Differential expression
785 of estrogen receptor subtypes and variants in ovarian cancer: effects on cell invasion, proliferation
786 and prognosis. *BMC Cancer* 2017;17:606.

- 787 [27] Lo R, Matthews J. A new class of estrogen receptor beta-selective activators. *Mol Interv.*
788 2010;10:133–6.
- 789 [28] Sieh W, Kobel M, Longacre TA, Bowtell DD, de Fazio A, Goodman MT, et al. Hormone-
790 receptor expression and ovarian cancer survival: an ovarian tumor tissue analysis consortium study.
791 *Lancet Oncol* 2013;14:853–62.
- 792 [29] Scarfone G, Bergamini A, Noli S, Villa A, Cipriani S, Taccagni G, et al. Characteristics of
793 clear cell ovarian cancer arising from endometriosis: a two center cohort study. *Gynecol Oncol*
794 2014;133:480-4.
- 795 [30] Guan B, Wang TL, Shih IeM. ARID1A, a factor that promotes formation of SWI/SNF-
796 mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. *Cancer Res*
797 2011;71:6718-27.
- 798 [31] Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, et al. ARID1A mutations in
799 endometriosis-associated ovarian carcinomas. *N Engl J Med.* 2010;14;363:1532-43.
- 800 [32] Yamamoto S, Tsuda H, Takano M, Tamai S, Matsubara O. Loss of ARID1A protein
801 expression occurs as an early event in ovarian clear-cell carcinoma development and frequently
802 coexists with PIK3CA mutations. *Mod Pathol* 2012;25:615-24.
- 803 [33] Ayhan A, Mao TL, Seckin T, Wu CH, Guan B, Ogawa H, et al. Loss of ARID1A expression is
804 an early molecular event in tumor progression from ovarian endometriotic cyst to clear cell and
805 endometrioid carcinoma. *Int J Gynecol Cancer* 2012;22:1310-5.
- 806 [34] Stamp JP, Gilks CB, Wesseling M, Eshragh S, Ceballos K, Anglesio MS, et al. BAF250a
807 Expression in atypical endometriosis and endometriosis-associated ovarian cancer. *Int J Gynecol*
808 *Cancer* 2016;26:825-32.

- 809 [35] Lowery WJ, Schildkraut JM, Akushevich L, Bentley R, Marks JR, Huntsman D, et al. Loss of
810 ARID1A-associated protein expression is a frequent event in clear cell and endometrioid ovarian
811 cancers. *Int J Gynecol Cancer* 2012;22:9-14.
- 812 [34] Shigetomi H, Tsunemi T, Haruta S, Kajihara H, Yoshizawa Y, Tanase Y, et al. Molecular
813 mechanisms linking endometriosis under oxidative stress with ovarian tumorigenesis and
814 therapeutic modalities. *Cancer Invest* 2012;30:473-80.
- 815 [35] Wiegand KC, Hennessy BT, Leung S, Wang Y, Ju Z, McGahren M, et al. A functional
816 proteogenomic analysis of endometrioid and clear cell carcinomas using reverse phase protein array
817 and mutation analysis: protein expression is histotype-specific and loss of ARID1A/BAF250a is
818 associated with AKT phosphorylation. *BMC Cancer* 2014;14:120.
- 819 [36] Anglesio MS, Bashashati A, Wang YK, Senz J, Ha G, Yang W, et al. Multifocal endometriotic
820 lesions associated with cancer are clonal and carry a high mutation burden. *J Pathol* 2015;236:201-
821 9.
- 822 [37] Vercellini P, Crosignani P, Somigliana E, Viganò P, Buggio L, Bolis G, et al. The 'incessant
823 menstruation' hypothesis: a mechanistic ovarian cancer model with implications for prevention.
824 *Hum Reprod* 2011;26:2262-73.
- 825 [38] Sanchez AM, Viganò P, Somigliana E, Panina-Bordignon P, Vercellini P, Candiani M. The
826 distinguishing cellular and molecular features of the endometriotic ovarian cyst: from
827 pathophysiology to the potential endometrioma-mediated damage to the ovary. *Hum Reprod*
828 *Update* 2014;20:217-3.
- 829 [39] Sanchez AM, Papaleo E, Corti L, Santambrogio P, Levi S, Viganò P, et al. Iron availability is
830 increased in individual human ovarian follicles in close proximity to an endometrioma compared
831 with distal ones. *Hum Reprod* 2014;29:577-83.

- 832 [40] Giacomini E, Sanchez AM, Sarais V, Beitawi SA, Candiani M, Viganò P. Characteristics of
833 follicular fluid in ovaries with endometriomas. *Eur J Obstet Gynecol Reprod Biol* 2017;209:34-8.
- 834 [41] Kobayashi H. Potential scenarios leading to ovarian cancer arising from endometriosis. *Redox*
835 *Rep.* 2016;21:119-26.
- 836 [42] Mangili G, Bergamini A, Taccagni G, Gentile C, Panina P, Viganò P, et al. Unraveling the two
837 entities of endometrioid ovarian cancer: a single center clinical experience. *Gynecol Oncol*
838 2012;126:403-7.
- 839 [43] Anglesio MS, Wang YK, Maassen M, Horlings HM, Bashashati A, Senz J, et al. Synchronous
840 endometrial and ovarian carcinomas: evidence of clonality. *J Natl Cancer Inst* 2016;108:djv428.
- 841 [44] Matsumoto T, Yamazaki M, Takahashi H, Kajita S, Suzuki E, Tsuruta T, et al. Distinct β -
842 catenin and PIK3CA mutation profiles in endometriosis-associated ovarian endometrioid and clear
843 cell carcinomas. *Am J Clin Pathol* 2015;144:452-63.
- 844 [45] Viganò P, Somigliana E, Chiodo I, Abbiati A, Vercellini P. Molecular mechanisms and
845 biological plausibility underlying the malignant transformation of endometriosis: a critical analysis.
846 *Hum Reprod Update* 2006;12:77-89.
- 847 [46] Stewart CJ, Leung Y, Walsh MD, Walters RJ, Young JP, Buchanan DD. KRAS mutations in
848 ovarian low-grade endometrioid adenocarcinoma: association with concurrent endometriosis. *Hum*
849 *Pathol* 2012;43:1177-83.
- 850 [47] Sato N, Tsunoda H, Nishida M, Morishita Y, Takimoto Y, Kubo T, et al. Loss of
851 heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial
852 cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid
853 carcinoma and clear cell carcinoma of the ovary. *Cancer Res* 2000;60:7052-6.

- 854 [48] Govatati S, Kodati VL, Deenadayal M, Chakravarty B, Shivaji S, Bhanoori M. Mutations in
855 the PTEN tumor gene and risk of endometriosis: a case-control study. *Hum Reprod* 2014;29:324-
856 36.
- 857 [49] Samartzis EP, Samartzis N, Noske A, Fedier A, Caduff R, Dedes KJ, et al. Loss of
858 ARID1A/BAF250a-expression in endometriosis: a biomarker for risk of carcinogenic
859 transformation? *Mod Pathol* 2012:885-92.
- 860 [50] Anglesio MS, Papadopoulos N, Ayhan A, Nazeran TM, Noë M, Horlings HM, et al. Cancer-
861 Associated Mutations in Endometriosis without Cancer. *N Engl J Med* 2017;376:1835-48.
- 862 [51] Chui MH, Wang TL, Shih IM. Endometriosis: benign, malignant, or something in between?
863 *Oncotarget* 2017;8:78263-4.
- 864 **[52] Berman JJ, Albores-Saavedra J, Bostwick D, Delellis R, Eble J, Hamilton SR, et al.**
865 **Precancer: a conceptual working definition -- results of a Consensus Conference. *Cancer***
866 ***Detect Prev.* 2006;30:387-94.***
- 867 [53] Vercellini P, Cribiù FM, Del Gobbo A, Carcangiu ML, Somigliana E, Bòsari S. The oncofetal
868 protein IMP3: a novel biomarker and triage tool for premalignant atypical endometriotic lesions.
869 *Fertil Steril.* 2013;99:1974-9.
- 870 [54] Wilbur MA, Shih IM, Segars JH, Fader AN. Cancer Implications for Patients with
871 Endometriosis. *Semin Reprod Med.* 2017;35:110-116.
- 872 [55] Kommoss F, Gilks CB. Pathology of Ovarian Cancer: Recent Insights Unveiling Opportunities
873 in Prevention. *Clin Obstet Gynecol.* 2017;60:686-696.
- 874 [56] Ogawa S, Kaku T, Amada S, Kobayashi H, Hirakawa T, Ariyoshi K, et al. Ovarian
875 endometriosis associated with ovarian carcinoma: A clinicopathological and immunohistochemical
876 study. *Gynecol Oncol.* 2000;77:298-304.

- 877 [57] Lopez N, Grabowski JP, De Santiago J, Zapardiel I. Carcinoma of the recto-vaginal septum.
878 Comprehensive literature review. *J Obstet Gynaecol.* 2016;36:450-4.
- 879 [58] Cozzolino M, Nasioudis D, Sisti G, Coccia ME. Malignant Transformation of Vaginal
880 Endometriosis - A Review of Literature. *Gynecol Obstet Invest.* 2017;82:105-112.
- 881 [59] Blanco LZ Jr, Kuhn E, Morrison JC, Bahadirli-Talbott A, Smith-Sehdev A, Kurman RJ.
882 Steroid hormone synthesis by the ovarian stroma surrounding epithelial ovarian tumors: a potential
883 mechanism in ovarian tumorigenesis. *Mod Pathol.* 2017;30:563-576.
- 884 [60] He ZX, Shi HH, Fan QB, Zhu L, Leng JH, Sun DW, et al. Predictive factors of ovarian
885 carcinoma for women with ovarian endometrioma aged 45 years and older in China. *J Ovarian Res*
886 *2017;10:45.*
- 887 [61] Tanase Y, Kawaguchi R, Takahama J, Kobayashi H. Factors that Differentiate between
888 Endometriosis-associated Ovarian Cancer and Benign Ovarian Endometriosis with Mural Nodules.
889 *Magn Reson Med Sci* 2017 Aug 21. doi: 10.2463/mrms.mp.2016-0149. In press.
- 890 [62] Taniguchi F, Harada T, Kobayashi H, Hayashi K, Momoeda M, Terakawa N. Clinical
891 characteristics of patients in Japan with ovarian cancer presumably arising from ovarian
892 endometrioma. *Gynecol Obstet Invest.* 2014;77:104-10.
- 893 [63] Kuo HH, Huang CY, Ueng SH, Huang KG, Lee CL, Yen CF. Unexpected epithelial ovarian
894 cancers arising from presumed endometrioma: A 10-year retrospective analysis. *Taiwan J Obstet*
895 *Gynecol* 2017;56:55-61.
- 896 **[64] Glanc P, Benacerraf B, Bourne T, Brown D, Coleman BG, Crum C, et al. First**
897 **International Consensus Report on Adnexal Masses: Management Recommendations. J**
898 **Ultrasound Med.** 2017;36:849-863.*

- 899 [65] Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation
900 at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet*
901 *Gynecol.* 2009;113:1027-37.
- 902 [66] Haraguchi H, Koka K, Takamura M, Makabe T, Sue F, Miyashita M, et al. Development of
903 ovarian cancer after excision of endometrioma. *Fertil Steril* 2016;106:1432-37.e2.
- 904 [67] Vercellini P, Frattaruolo MP, Buggio L. Toward minimally disruptive management of
905 symptomatic endometriosis: reducing low-value care and the burden of treatment. *Expert Rev*
906 *Pharmacoecon Outcomes Res.* 2017 Dec 6:1-4. doi: 10.1080/14737167.2018.1411803. In press.
- 907 [68] Kho RM, Abrao MS. Ovarian remnant syndrome: etiology, diagnosis, treatment and impact of
908 endometriosis. *Curr Opin Obstet Gynecol.* 2012;24:210-4.
- 909 [69] Vercellini P, Facchin F, Buggio L, Barbara G, Berlanda N, Frattaruolo MP, et al. Management
910 of Endometriosis: Toward Value-Based, Cost-Effective, Affordable Care. *J Obstet Gynaecol Can.*
911 2017 Oct 5. pii: S1701-2163(17)30684-9. doi: 10.1016/j.jogc.2017.07.011. In press.
- 912 [70] Vercellini P, DE Matteis S, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Long-term
913 adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review
914 and meta-analysis. *Acta Obstet Gynecol Scand.* 2013;92:8-16.
- 915 [71] Koga K, Takamura M, Fujii T, Osuga Y. Prevention of the recurrence of symptom and lesions
916 after conservative surgery for endometriosis. *Fertil Steril.* 2015;104:793-801.
- 917 [72] Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Fedele L. 'Blood On The Tracks'
918 from corpora lutea to endometriomas. *BJOG.* 2009;116:366-71.
- 919 **[73] Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral**
920 **contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with**
921 **and without endometriosis. *Am J Obstet Gynecol.* 2004;191:733-40.***

- 922 [74] Malvezzi M, Carioli G, Rodriguez T, Negri E, La Vecchia C. Global trends and predictions in
923 ovarian cancer mortality. *Ann Oncol.* 2016;27:2017-2025.
- 924 [75] La Vecchia C. Ovarian cancer: epidemiology and risk factors. *Eur J Cancer Prev.* 2017;26:55-
925 62.
- 926 [76] Pearce CL, Stram DO, Ness RB, Stram DA, Roman LD, Templeman C, et al. Population
927 distribution of lifetime risk of ovarian cancer in the United States. *Cancer Epidemiol*
928 *Biomarkers Prev* 2015;24:671-676.*
- 929 [77] Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk
930 reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal
931 women. *Gynecol Oncol.* 2015;139:487-94.*
- 932 [78] National Institute for Health and Care Excellence. Endometriosis: diagnosis and management.
933 NICE guideline NG73. September 2017. [https://www.nice.org.uk/guidance/ng73/evidence/full-](https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315)
934 [guideline-pdf-4550371315](https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315) [Accessed 11 December 2017].
- 935 [79] Sainz de la Cuesta R, Eichhorn JH, Rice LW, Fuller AF Jr, Nikrui N, et al. Histologic
936 transformation of benign endometriosis to early epithelial ovarian cancer. *Gynecol Oncol*
937 1996;60:238-44.
- 938 [80] Sainz de la Cuesta, Izquiero M, Canamero M, Granizo JJ, Manzarbeitia F. Increased prevalence
939 of p53 overexpression from typical endometriosis to atypical endometriosis and ovarian cancer
940 associated with endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2004;113:87-93.
- 941 [81] Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease
942 emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. *Adv Anat Pathol*
943 2007;14:241-60.
- 944 [82] Wald NJ. The definition of screening. *J Med Screen.* 2001;8:1.

- 945 [83] Narod SA, Sopik V, Giannakeas V. Should we screen for ovarian cancer? A commentary on
946 the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) randomized trial. *Gynecol*
947 *Oncol.* 2016;141:191-194.
- 948 [84] Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on
949 ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening
950 Randomized Controlled Trial. *J Am Med Assoc* 2011;305:2295–303.
- 951 **[85] Pinsky PF, Yu K, Kramer BS, Black A, Buys SS, Partridge E, Gohagan J, Berg CD,**
952 **Prorok PC. Extended mortality results for ovarian cancer screening in the PLCO trial with**
953 **median 15years follow-up. *Gynecol Oncol.* 2016;143:270-275.***
- 954 [86] Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer
955 screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a
956 randomised controlled trial. *Lancet.* 2016;387:945-956.
- 957 [87] Thornton H. Communicating the benefits, harms and risks of medical interventions: in
958 journals; to patients and public. *Int J Surg.* 2009;7:3-6.
- 959

960 TABLE 1. Common molecular patterns in endometriosis-associated carcinomas.

Endometriosis-associated ovarian clear cell carcinoma	Endometriosis-associated ovarian endometrioid carcinoma
<p>Mutations in</p> <ul style="list-style-type: none"> • <i>ARID1A</i> • <i>PIK3CA</i> • <i>CTNNB1</i> • <i>PTEN</i> <p>Expression of</p> <ul style="list-style-type: none"> • HNF-1beta ++ • BAF250a -- • Napsin A ++ • Nuclear ERα -- • Cytoplasmatic ERβ2 -- • Cytoplasmatic ERβ5 -- 	<p>Mutations in</p> <ul style="list-style-type: none"> • <i>PTEN</i> • <i>CTNNB1</i> • <i>KRAS</i> • <i>ARID1A</i> • <i>PIK3CA</i> • <i>PPP2R1A</i> <p>Expression of</p> <ul style="list-style-type: none"> • BAF250a --

961

962 TABLE 2. A conceptual definition of premalignant lesions based on five diagnostic criteria
963 developed during the National Cancer Institute Consensus Conference on Precancer.
964 November 8–9, 2004, George Washington University Medical Center, Washington, DC.

965

- 966 (1) Evidence exists that the precancer is associated with an increased risk of cancer.
- 967 (2) When a precancer progresses to cancer, the resulting cancer arises from cells within the
968 precancer.
- 969 (3) A precancer is different from the normal tissue from which it arises.
- 970 (4) A precancer is different from the cancer into which it develops, although it has some, but not
971 all, of the molecular and phenotypic properties that characterize the cancer.
- 972 (5) There is a method by which the precancer can be diagnosed.

973

974 From Berman *et al.* [52]

975

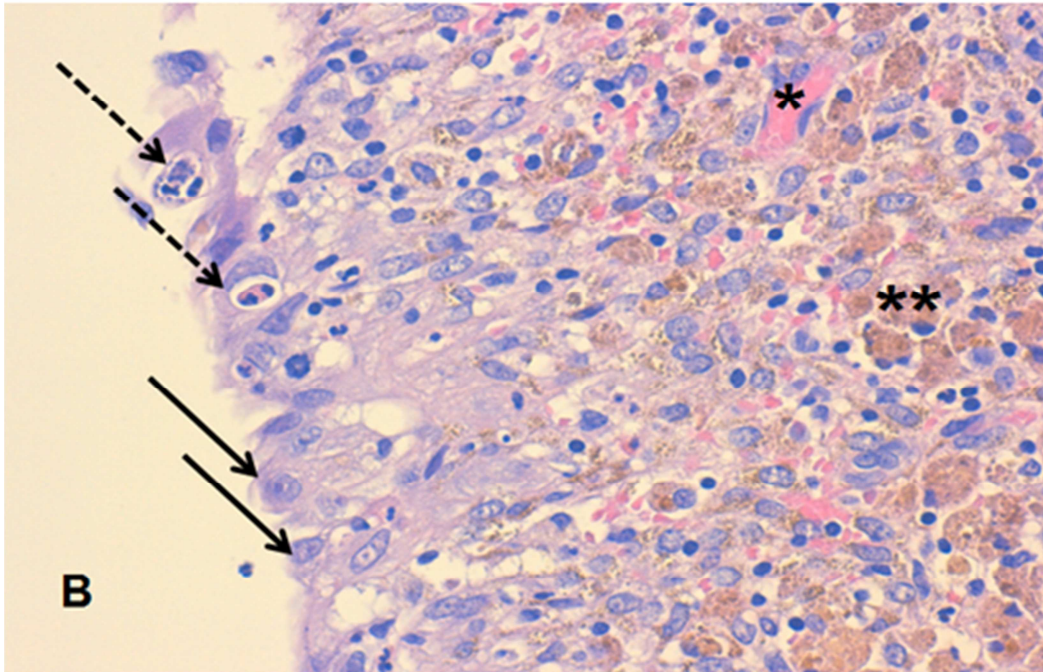
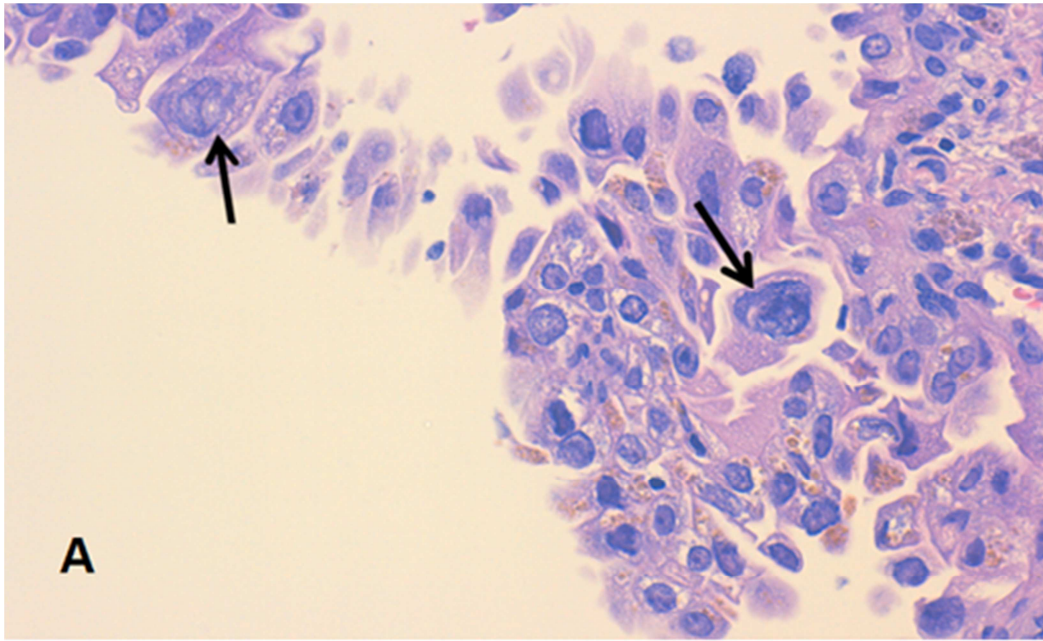
976 LEGEND TO FIGURE 1

977

978 1A. A high-power image of an endometriotic cyst wall with atypical cells showing eosinophilic
979 cytoplasm, large hyperchromatic (arrows) or pale nuclei with moderate pleomorphism, increased
980 nucleus-to-cytoplasm ratio, mitosis, and cellular crowding, stratification, or tufting.
981 (hematoxylin and eosin, original magnification 40x).

982

983 1B. High-power image of an endometriotic cyst wall showing hyperplastic epithelial cells
984 exhibiting uniform reactive atypia with variable nuclear features: increased nucleus-to-cytoplasm
985 ratio, pale nuclei with slight pleomorphism, prominent nucleoli (arrows) and acute inflammatory
986 cells within the epithelium (dotted arrows). The endometriotic stromal cells are admixed with acute
987 and chronic inflammatory cells; * prominent capillaries; ** hemosiderin laden macrophages.
988 (hematoxylin and eosin, original magnification 40x).



HIGHLIGHTS

- Endometriosis is associated with a moderate increase in ovarian cancer risk
- In women with endometriosis the risk of endometrioid ovarian cancer is doubled
- The risk of ovarian cancer is associated with age and endometriotic cyst dimension