Abstract

Peri /postmenopausal endometriosis is not as rare as once we thought. Accumulated data revealed that around 1/3-1/4 of women with surgically-diagnosed endometriosis after the age of 40. The uneasiness of the issue of malignant transformation or malignancy in such women created a challenge for us. Here the management strategy for women with endometriosis after the age of 40 is discussed in the light of scientific evidence.

Key words: Endometriosis, perimenopause, menopause, endometriosis associated ovarian cancer (EAOC), Pain, Infertility

INTRODUCTION

Endometriosis is defined as the presence of endometrial tissue outside the uterus. It is one of the most peculiar diseases in medicine; we still do not know how it happens, what its course is during the years, whether it will inhibit fertility or -as recently gained much focus on- it will cause malignant disease. Since estrogen plays a central role in endometriosis, for many years it has been thought that "endometriosis is the disease of fertile years". With the accumulation of data, we have realized that "there is no age limit" for endometriosis. However, the management of endometriosis differs according to the age due to changing "demands" of the patient and "concerns" of the medical professional.

Endometriosis at older ages is clinical challenge especially for those at menopausal transition. In 1993, attention was especially drawn to perimenopausal women for by Witt and Barad (1). Thereafter there have been some reports mainly case reports and case series, a few reviews and few clinical studies on peri and postmenopausal endometriosis.

Here we aimed to review the "challenging" management of women with endometriosis after the age of 40 in the light of available data.

Endometriosis is not "limited to" reproductive ages

Endometriosis is a common gynecological disease and it prevalence is about 1 in 10 women. Although it is well known that estrogen is cine-qua-non for endometriosis, it may be found at any age of a woman. The first report on postmenopausal endometriosis was a case report of 78-year-old woman by Edgar Haydn in 1942(2). According to big-series of Haas et al, (3), of total 42,079 women histologically proven endometriosis, there were 13.985 patients (33.23 %) in the perimenopausal age group (40–50 years), and 2.984 (7.09 %) patients in the postmenopausal age group(50–95 years). In another study from Ireland, of 1383 women surgically proven endometriosis, the proportion of cases after the age of 40 is 27.4% (4). It was also shown that for the age 40 and above, the age-specific incidence has been increased in years (4). Thus perhaps it may be assumed that when the awareness increases, the diagnosis and incidence of endometriosis after the age of 40 may be increased with time. In our study (Oral E et al, submitted), we have found that endometrioma was the most common benign adnexial mass among 1100 women at the age 40 and above. According to the literature, prevalence of postmenopausal endometriosis is about 2-5% (5).

Confronting the problems in women with endometriosis after the age of 40

Is menopause at earlier age?

According to scarce available data, both surgery for endometriomas and also endometriosis per se may opt women to have earlier menopause (6).Thus, although the onset of menopause at the age 40-45 and before 40 are accepted as early menopause and premature menopause, respectively, these are not uncommon among women with endometriosis especially with a history of infertility (7).

Fertility issues

Since women anticipate high level carrier in contemporary lifestyle, usually fertility is postponed until the ages of late30s and early 40s. Thus, especially in women with endometriosis may be obliged to

face the fertility problems mainly due to low ovarian reserve. Apart from the endometriosis itself, concomitant problems such as adenomyosis and myoma may contribute to fertility problem (figure 1). We ironically call this as “dragon’s triangle”.

Pain

Pain is one of the major symptoms in endometriosis. Although decreasing estrogen levels in older ages may alleviate this symptom, peripheral or local production of estrogens as well as external estrogens such as hormonal treatments may cause exacerbation of the symptom even in women who had radical surgery for endometriosis. Pain persistence or recurrence are important problems even at age >40. According to 72 postmenopausal women (age 46-79) with endometriosis from a single institution, one of the two most common symptoms at presentation was abdominal pain (26.4%) (8).

Malignancy issue

The first report on malignant transformation of the endometriotic tissue was described by Sampson in 1925 (9). For last couple of years, malignancies especially ovarian carcinoma associated with or stemmed from endometriosis gained much attention. It is now accepted that malignant transformation of endometriosis occurs -mostly in the ovaries- in 1-3% cases (10).The continuum to malignancy of ovarian carcinoma from atypical endometriosis has been unveiled in years since the first report of 5 cases (three clear cell carcinomas, two endometrioid carcinomas) in 1988 by LaGrenade and Silverberg (11,12). Significant increase in the relative risk (RR) of clear cell (RR: 3.37, CI: 1.24-9.14), and endometrioid type (RR: 2.53, CI:1.19-5.38) ovarian carcinoma has been reported in women with endometrioma after at least 5 years from the diagnosis (13). There is some evidence that such malignant transformation occurs during the perimenopausal period (14).Moreover, in a recent report, Murakami et al. (15) searched the cases of ovarian carcinoma stemmed from endometriotic cyst in the literature starting from year 2000. They have found that the median time from the diagnosis of the cyst to diagnosis of the carcinoma was 36 months and they have bravely suggested that when the cyst was found it might already have the malignant cells in it.

Although there is still no definite marker to confirm or exclude malignancy, for women with suspicion of malignancy, human epididymal secretory protein (HE4) is important, especially combined with CA-125 as ROMA index is accepted as the most efficient biomarker today (16).

In our retrospective analysis we have also drawn attention to the probable continuum of the pathological way from endometriosis to atypical endometriosis and ovarian carcinoma. Of 661 women with ovarian carcinoma or borderline ovarian tumor, 48 (4.7%) had endometriosis and of those 48, 73% had atypical endometriosis (17). Recently we have also found Endometrioma-associated ovarian tumors were developed in nearly 11% of women with endometrioma (Oral E et al, submitted). The risk of ovarian cancer is especially higher in women with longstanding (more than 10 years) endometriosis, or recurrent endometrioma, newly diagnosed endometrioma (10).

Menopausal Symptoms

Women with endometriosis may have an inauguration of menopause by medical or surgical means. In addition, usually they tend to have earlier spontaneous menopause as mentioned above. These facts may lead to abrupt fall in the estrogen levels and cause severe menopausal symptoms(18). Thus, this is important problem especially when we consider women with endometriosis after the age of 40.

Management of fertility problems in women with endometriosis after the age of 40

Endometriosis is a cause of subfertility via different suggested mechanisms such as diminished ovarian reserve, poor oocyte quality, tubal problems, fertilization and implantation problems even sperm problems (19-21). For women over 40 years of age, diminished ovarian reserve seems to be utmost important. It is known that age, previous surgery for endometrioma and also endometrioma per se are important factors may contribute to diminished ovarian reserve in such women. Though management should include IVF for women over 40, the first step should be ovarian reserve testing so that deciding whether to perform embryo pooling or not. After having the embryos frozen, ovarian suppression by GnRH-analogs should be commenced followed by frozen-thawed embryo transfer (figure 2).

Management of pain problems in women with endometriosis after the age of 40

Management of pain in women with endometriosis over 40 is again dependent on fertility desire. If so, women are to be offered IVF treatment. If pain is the only complaint surgery is to be the first management option due to the risk of malignant transformation and malignancy (Figure 3).

If there is medical (eg. cardiovascular disease, pulmonary disease etc.) or surgical (previous multiple operations) contraindications for a surgical approach and there is no sign for malignancy, then medical treatment is to be considered. According to data we have at the moment there are many medical options for treatment of endometriosis, basically; Gonadotropin releasing hormone agonists (GnRH-a), Progestogens, or Aromatase Inhibitors (AIs), Gonadotropin releasing hormone antagonists (GnRH-ant), combined oral contraceptives (COCs), Levonorgestrel intrauterin system(LNG-IUS) can be used for women with endometriosis after the age 40.

Management of Menopausal symptoms in women with endometriosis after the age of 40

When the women with endometriosisdo have menopausal symptoms, there may be two concerns on each pan of the scale; one is basic menopausal concerns (bones, brain, cardiovascular system, and quality of life especially in terms of vasomotor and vulvo-vaginal problems) and the second one is the risk of recurrence and malignancy (22, 23). As recently reviewed and concluded by Zanello et al (23), "*women should not be denied the replacement therapy solely due to endometriosis*". Women with vasomotor symptoms, especially when they experience early or premature menopause may use hormonal treatment. The drug to be selected should be combined estrogen and progestogen unrelated to being surgically

menopausal or not, since estrogen only regimens may activate the residual endometriotic foci even in women after surgery for endometriosis. There are also some implicative reports on malignant transformation (24). If the surgical procedure is selected, hysterectomy and bilateral salpingooopherectomy and excision of the visible endometriotic foci should be preferred since the risk of recurrence is higher with suboptimal surgery(25). Another important point is that, if the woman with endometriosis needs tamoxifen treatment, the risk of malignant transformation should be considered (22).

Asymptomatic patient in women with endometriosis after the age of 40

We do not know the exact prevalence of asymptomatic endometriosis at any age. The management is also quite blurred for asymptomatic patients with endometriosis. Asymptomatic endometriosis may be found by chance via imaging methods –mainly by ultrasound-or during the operations for other reasons. Although in 1996, Eric J Thomas has suggested a challenging opinion of his own by writing "*Asymptomatic endometriosis is likely to be a physiological phenomenon of very limitedrelevance both physician and the patient.*" (26) and finished his paper by referring "an unidentified Edinburg physician's quote "*It is a very very clever doctor who can make an asymptomatic patient feel better*", there are some recent "warning" articles on asymptomatic patient with endometriosis. In their very recent retrospectively analyzed case series, Son JH et al (27) reported 50 women with ovarian clear cell carcinoma. Of those, 11 were women with asymptomatic endometrioma and being under regular gynecological examination. The authors suggested yearly close surveillance from the age mid30s in patients with asymptomatic endometrioma.

Adenomyosis in women after the age 40

Although it has been thought that adenomyosis is a different disease from endometriosis, however it has been suggested that it might be a "variant" rather than a disease (28). As shown in figure 1, co-existence of adenomyosis and endometriosis as well as myoma is common. The presentation may be abnormal uterine bleeding, pelvic pain or fertility problems. At the age of 40 and above, management is similar to the one at fertile ages. If the uterus is to be preserved, GnRH-a suppression or progestogens (especially Levonogestrel intrauterine system) may be appropriate treatment modalities. There are also uterus-sparing novel surgical options to excise the adenomyotic tissue (29). Nevertheless, most women with adenomyosis after 40 presenting with pain or abnormal bleeding instead of fertility problems, thus total hysterectomy should be offered.

CONCLUSION

Management of endometriosis in women over 40 years of age is challenging. Infertility or pain may be the major problems, or even there may be asymptomatic endometrioma. We need more data on women with asymptomatic or accidentally found endometrioma. Treatment of fertility problems or pain should be accordingly. The accumulated data on atypical endometriosis leading to endometriosis associated malignancy should be remembered in those women, thus surgical management may be more liberally chosen.

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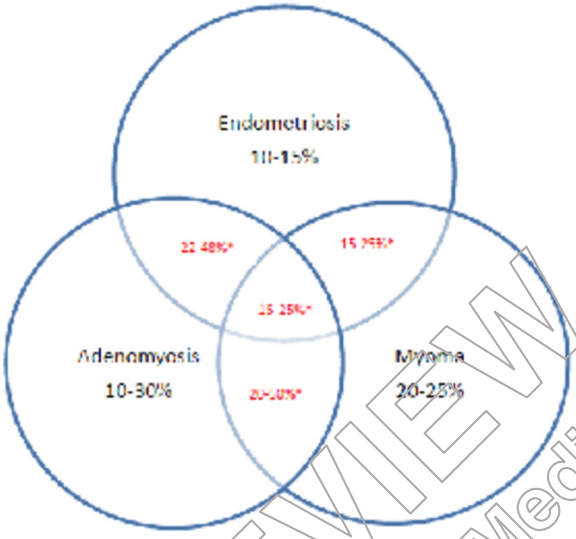

Figure 1: DRAGON's TRIANGLE

*: co-prevalance rate

(Modified from the work of Prof Michel Mueller, Switzerland)

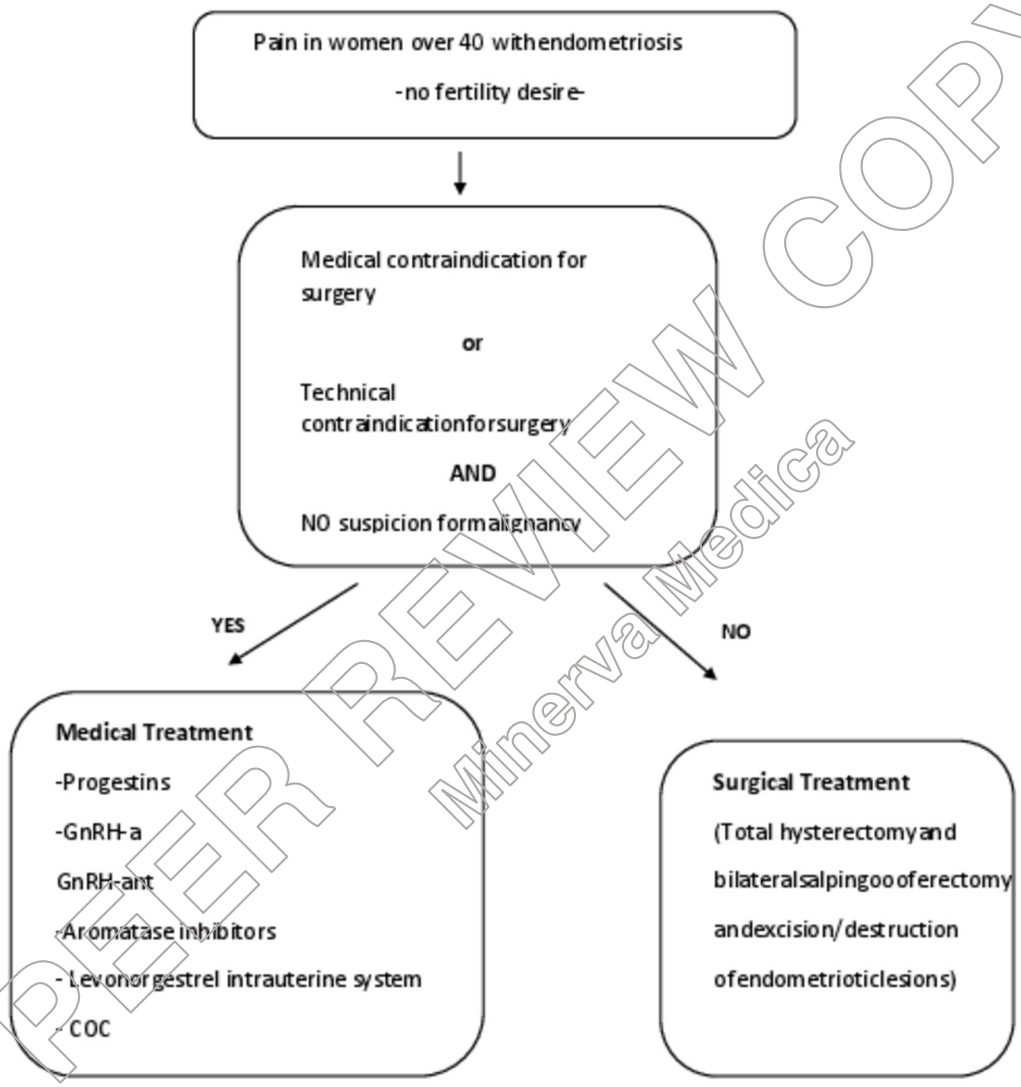

Figure 2: Algorithm for pain management for women with endometriosis over the age of 40.

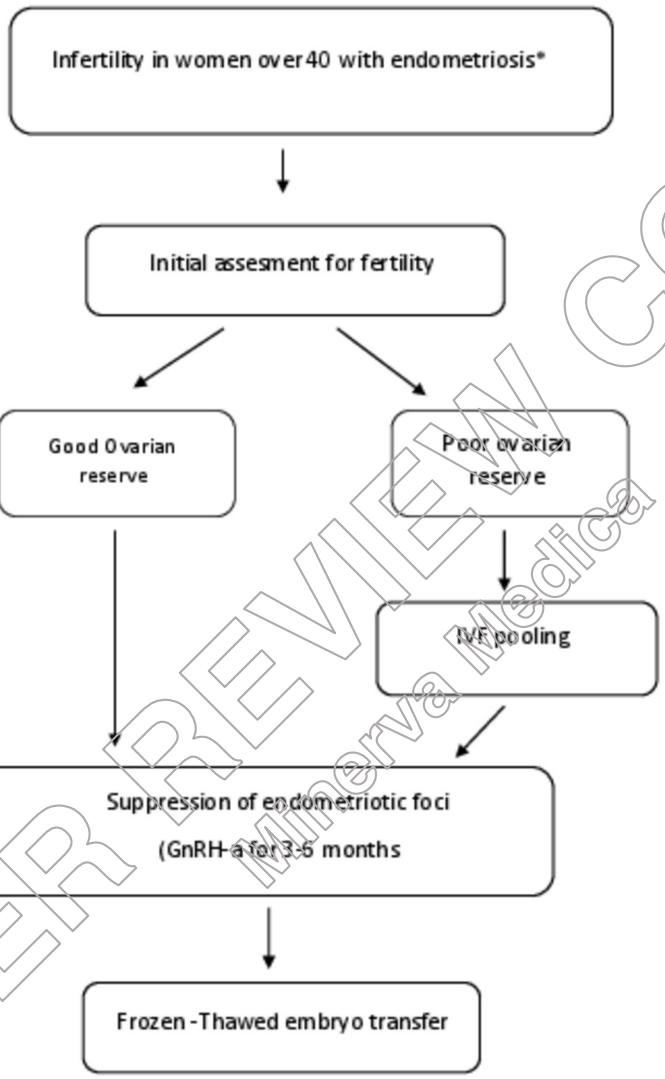

Figure 3: Algorithm infertility management for women with endometriosis over the age of 40.

*: "Surgery" should be chosen in the management of women with suspicious malignancy