Early stage management of ovarian endometrioma to prevent infertility

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Abstract

There are now convincing data showing that cystectomy of the endometrioma is not only no cure of infertility, but may harm follicle reserve. The question arises why is cystectomy for an endometrioma, in contrast with other benign cysts, a risk for follicle reserve and how can ovarian damage be prevented.

Surgical specimens of ovaries with endometrioma in situ show in the majority of cases manifestly a combined extra-ovarian and intra-ovarian pathology with the cortex invaginated to form a pseudocyst. The extra-ovarian pathology includes endometrial lining of the cortex, bleeding and adhesions with surrounding tissues. The intra-ovarian pathology is characterized by microscopic stromal implants, fibrosis, smooth muscle metaplasia and arteriosclerosis, all affecting follicle reserve in the endometrioma bed.

Clinically, ovarioscopy allows differential diagnosis (e.g. luteal cyst) and evaluation of the degree of fibrosis and darkening of the cortical wall. Transvaginal colour Doppler sonography can demonstrate the presence and extent of devascularisation in the endometrioma bed. Given this reality, surgery should be based on evaluation of the pathology of the endometrioma bed, but not on the mere size of the chocolate cyst. The main clinical problem is indeed the delayed diagnosis and consequently advanced irreversible cortical damage. Therefore, the sooner endometriomas are diagnosed, the better, because it increases the chances that vascularisation of the endometrioma bed is preserved. Finally, ablation, but not excision is the treatment of choice.

The diagnosis of endometriosis is traditionally based on laparoscopy, but in a sexually active adolescent transvaginal endoscopy can be proposed.

Key words: Endometrioma, vascularisation, diagnosis, surgery, follicle reserve, fertility.

Introduction

Endometriosis in adolescents can be described as a Mona Lisa face, where a mysterious smile covers a hidden disease that tragically threatens to destroy the perspective of a healthy reproductive life. The discussion of the facts, views and vision on endometriosis in the adolescent and young woman is a challenging and critical issue for understanding the disease process and its management.

While few data are available on the onset of endometriosis in adolescents, recent studies have documented a variety of forms ranging from a disease with subtle peritoneal lesions, up to severe rASRM stages III and IV with inclusion of ovarian endometriomas (Brosens et al., 2013). Menstrual-related complaints in these patients are common, elicit compassion, but only rarely stimulate a search for the presence of endometriosis. The clinical reality is that complaints of dysmenorrhoea or acyclic pelvic pain may hide a disease with a severity that is not reflected by the degree of discomfort and that may have already reached a stage where future reproductive life of an otherwise healthy adolescent is severely compromised. Especially in these young women, endometriosis remains a disease with a delayed diagnosis, mainly because non-invasive tools for a reliable diagnosis are not available. Very little is known on the true incidence of adolescent endometriosis because the necessity of laparoscopy for diagnosis severely biases any serious evaluation.

This paper intends to elucidate the pathological and clinical features of adolescent endometriosis and discuss new perspectives on diagnosis and
The risk of severe ovarian endometriosis in adolescents

While the symptoms of endometriosis will often start at a young age, even before the onset of menstruation, the diagnosis by laparoscopy is almost always postponed for several years. Laufer et al. (1997) provided a dramatic insight on reasons for such a delay in adolescents. They mention that in their 32 cases classic adult symptoms were observed in only 9.4% of the adolescents, with 28.1% having acyclic and 65.5% both cyclic and acyclic pain. They also found that adolescents with endometrioma were more likely to have experienced an early menarche and have regular menses than those without the condition.

There are reasons to believe that such a delay may cause serious damage in young women and impair their future fertility. It is true that we cannot predict in which case the disease will indeed progress, but – given the present delay in diagnosis – when symptoms persist for years there is a clear possibility that the disease will progress. Especially worrying is the presence of an ovarian endometrioma that may be asymptomatic. Indeed, out of a total of 403 cases classified according to rASRM described in the literature, by age 20 or less, 147 (or 35%) were stage III or IV, although severity greatly differed among studies (Brosens et al., 2013). This is indirect, but strong evidence of a tendency of the disease to progress and produce early damage.

Recent progress

Progress in endometriosis research has in recent years established two important facts: first, the delay in diagnosing endometriosis in patients with and without symptoms and secondly the ovarian endometrioma is associated with a major risk of follicle loss whether or not surgery is performed.

Delay of diagnosis

Several studies have documented the delay of diagnosis in women with endometriosis. Anglo-American as well as European and Latin American studies have shown a delay from 3 to 11 years between the onset of pain symptoms and the final diagnosis of endometriosis (Table I). Arruda et al. (2003) found that the median time period between onset of symptoms and diagnosis was 4.0 (2.0-6.0) years for women whose main complaint was infertility, but 7.4 (3.6-13.0) years for those with pelvic pain. Hudelist et al. (2012) found a median interval from the first onset of symptoms to diagnosis of 10. 4 (SD: 7.9) years. The majority of patients received at least one wrong diagnosis. Clearly, the delay in diagnosis of endometriosis is unacceptable, especially for young women with pelvic pain. There are several reasons for explaining this delay, starting with a reluctance to disclose problems associated with menstruation, but the main obstacle is that to confirm a diagnosis laparoscopy is necessary. The study of Ballard et al. (2006) highlighted the importance of an early diagnosis for women who suffer at physical, emotional, and social levels when they remain undiagnosed.
45.7% of these cases (including 3 with genital malformations), with an average recurrence time of 33.4 months. Four people got pregnant after treatment. Interestingly, recurrence occurred in (1) 60% of 15 adolescents who were not treated post-operatively, (2) 46% of 13 who received an oral contraceptive medication, (3) 1 of the 2 subjects given a progestin and (4) none of the 5 treated with a GnRH analogue (GnRHA). The difference between untreated and GnRHA-treated subjects was statistically significant (P = 0.038). The authors concluded that adolescent endometriosis deserves a much greater attention.

Views on pathogenesis

The most common theories on the pathogenesis of endometriosis include implantation and metaplasia. Both mechanisms may be involved and explain the observations on the process of early onset endometriosis and progression of ovarian endometrioma formation.

Neonatal uterine bleeding as a potential cause of early onset endometriosis

In a recent paper we elaborated on a new theory to explain pelvic endometriosis, including in premenarcheal girls, based on the finding that the neonatal endometrium can display secretory activity immediately after birth and, in some cases, changes analogous to those seen at menstruation in adults (Brosens and Benagiano, 2013) (Table II). The neonatal uterus is therefore capable of shedding its endometrium and, indeed, visible neonatal bleeding occurs in circa 5% of the neonates, while occult bleeding can be detected in the majority of cases. Retrograde uterine bleeding may be favoured by the greater length of the cervix than the corpus and the presence of a functional plugging of the endocervical canal by thickened mucus in the neonate. Ectopic endometrial implantation in a newborn with hydrometrocolpos has been documented (Arcellana et al., 1996). These data, coupled to the observation of a significantly increased risk of endometriosis in adolescents with cervical outflow obstruction by uterine anomalies and patent Fallopian tubes, indicate that endometriosis, especially in children and young adolescents, may originate from retrograde uterine bleeding soon after birth.

It is clear that this theory needs to be further explored by investigation of the presence of endometrial stem cells in the endometrial sheddings at the time of neonate uterine bleeding.

Detrimental effect of the endometrioma on follicle reserve

Although the ovarian endometrioma is described as an ovarian cyst the pathology is completely different from other benign ovarian cysts. The vast majority of endometriomas are not intraovarian cysts, but pseudocysts formed by invagination of the ovarian cortex and occlusion by adhesions (Hughesdon, 1957). The so-called typical site of rupture as described by Sampson (1922) in his series of 37 endometriotic cysts, represents the site of inversion of the pseudocyst. In contrast with benign ovarian cysts like teratoma or benign cystoma, there is no plane of cleavage and follicular images are
absent in the wall of the cyst (Maneschi et al., 1993). Pathological progression occurs in the interstitial endometrioma bed and is manifested by smooth muscle metaplasia and hyperplasia, devascularisation and follicle loss (Fukunaga, 2000).

With the aid of a nude mouse model van Kaam et al. (2008) were able to demonstrate that, as soon as one week after inoculation with human endometrium, alpha-smooth muscle actin expression is induced in the surrounding murine fibroblasts, whereas no expression was observed in the human cells. These findings strongly suggest that the presence of smooth muscle-like tissue in so-called deep endometriosis or adenomyoma lesions is accounted for by a reaction of the local environment to the presence of ectopic endometrium rather than smooth muscle metaplasia of the ectopic endometrium itself.

In a recent study Kuroda et al. (2012) evaluated biopsies from healthy adherent ovarian tissue in women with endometrioma and in those with non-endometriotic cysts. The study demonstrated that the density of follicles in ovarian tissue from the endometrioma bed is approximately one- to two-thirds of that adjacent to a non-endometriotic cyst in women younger than 35 years. It remains, however, to be shown whether a biopsy from the ovarian wall after cystectomy is sufficient for evaluating the extent of metaplasia, vascular sclerosis and loss of follicles in the endometrioma bed. Cystectomy of the pseudocyst wall not only will remove these remaining primordial follicles aggressively, but extensive coagulation for haemostasis following cystectomy may damage the blood supply towards the affected ovary irreversibly, resulting in a permanent unresponsiveness of that ovary to endogenous hormonal stimulation, i.e. in premature ovarian failure.

Proactive management of cystic ovarian endometrioma to preserve fertility

The goal of proactive management of cystic ovarian endometrioma is to ablate the endometrial tissue from the endometrioma before devascularisation and follicle loss in the endometrioma bed have occurred. Therefore the present generalised delay in diagnosis needs to be corrected through early diagnosis in adolescent or young women with chronic pelvic pain.

First line approach

NSAIDs are the first line treatment for primary dysmenorrhoea and act by inhibiting cyclo-oxygenase-protein expression and consequently prostaglandins production, but their efficacy in endometriosis is not well documented. Oral contraceptives or continuous progestogen can be used for 3 to 6 months. Several studies have shown that in the absence of a clear effect of NSAIDs with normalisation of daily and school activities, there is a 70% risk of endometriosis (Reese et al., 1997; Laufer et al., 1997). Today there is an active search for biomarkers for diagnosing endometriosis and in a recent case-control study of infertile women Mihalyi et al. (2010) measured plasma concentrations of interleukin-6, tumour necrosis factor-alpha, high-sensitivity C-reactive protein and cancer antigens CA-125 and CA-19-9. They found that measurement of these six selected biomarkers obtained during the secretory phase, or during menstruation allows the diagnosis of both minimal-mild and moderate-severe endometriosis with high sensitivity and clinically acceptable specificity. However, in the absence of clinical validation, the usefulness of a biomarker or set of biomarkers for the diagnosis of endometriosis remains questionable.

At present general practitioners can have a crucial effect on the patient’s present and future quality of general and particularly reproductive life by maintaining a high index of suspicion, initiating medical treatment and referring when needed.

Is ultrasound useful?

Cystic endometriosis is assumed to occur rarely in the adolescent. However, the criterium to diagnose the ovarian endometrioma by ultrasound is based on a size which may be representative in the adult, but not in the adolescents. The smaller endometriomas in adolescents may be assumed to represent dysfunctional ovarian cysts and therefore laparoscopy is not performed. On the other hand, the diagnosis of smaller endometriomas is critical for the proactive treatment of the ovarian endometrioma to prevent the associated irreversible damage in the endometrioma bed.

Recently, Qiu et al. (2012) have documented by transvaginal colour Doppler sonography the stages of ovarian interstitial blood flow in the endometrioma bed. This technique may predict the endometriotic cyst-induced arteriosclerosis and devascularisation in the endometrioma bed.

Pelvic endoscopy in the adolescent

The diagnosis of endometriosis is traditionally based on laparoscopy, but in a sexually active adolescent transvaginal endoscopy can be proposed. The technique has several advantages for both patient and surgeon. For the adolescent it can be important to avoid any surgical scarring in the navel area. The
clinical advantages include the direct access to the ovaries, the inspection under hydrofloatation avoiding collapse of adhesions and observation of microvascularisation on the whitish ovarian surface. Finally, in most cases the direct access to the site of inversion and adhesions of the endometrioma in the ovarian fossa allows for access to the endometrioma cavity and ablation of the endometriotic and vascular tissue by the use of a bipolar probe (Fig. 1). Cysts larger than 3-5 cm are a contraindication for a transvaginal endoscopic approach.

Conclusion: future of clinical and basic research

The ovarian endometrioma has a complex structure that requires evaluation of the cystic structure with adhesions by endoscopy and the extent of endometrioma bed devascularisation by 3D-Doppler sonographic evaluation. The technique is critical for evaluating the prognosis of resection versus ablation and risk of follicle loss.

References


