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Short title: Adolescent endometriosis

Progress in the diagnosis and management of adolescent endometriosis: an opinion

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Key message

Early onset endometriosis may have a different origin than the adult variant, originating from neonatal uterine bleeding. It can be progressive and severe and, if left untreated, may jeopardise future fertility of a young patient. It requires early diagnosis and appropriate stepwise minimally invasive management, medical, surgical or combined.

HIGHLIGHTS

- Early-onset endometriosis (EOE) should be considered as a specific form with its own pathophysiology, symptomatology and risk factors.
- EOE may originate from neonatal uterine bleeding through the seeding of naïve endometrial progenitor cells into the pelvic cavity around birth.
- EOE can be progressive, thereby posing a threat to the future reproductive capacity of the young woman.
- Symptomatology is often nonspecific and there is a need for new, simple, non-invasive markers of an increased risk.

- When imaging gives rise to suspicion of severity, a stepwise, minimally invasive approach should be utilized.

Abstract

Increasing evidence indicates that early onset endometriosis (EOE), starting around menarche or early adolescence, may have an origin different from the adult variant, originating from neonatal uterine bleeding (NUB). This implies seeding of naïve endometrial progenitor cells into the pelvic cavity with NUB; these can then activate around thelarche. It has its own pathophysiology, symptomatology and risk factors, warranting critical management re-evaluation. It can also be progressive, endangering future reproductive capacity. This variant seems to be characterized by the presence of ovarian endometrioma. Today, the diagnosis of endometriosis in young patients is often delayed for years; if rapidly progressive, it can severely affect pelvic organs, even in the absence of serious symptoms. Given the predicament, great attention must be paid to symptomatology that is often non-specific, justifying a search for new, simple, non-invasive markers of increased risk. Better use of modern imaging techniques will aid considerably in screening for the presence of EOE. Traditional laparoscopy should be limited to cases in which imaging gives rise to suspicion of severity and a stepwise, minimally invasive approach should be used, followed by medical treatment to prevent recurrence. In conclusion, EOE represents a condition necessitating early diagnosis and stepwise management, including medical treatment.

KEYWORDS: adolescents, dysmenorrhea, endometrioma, endometriosis, pelvic pain

Author biography

Giuseppe Benagiano is Professor Emeritus at 'la Sapienza', University of Rome, where he previously held positions of Director, First Institute of Obstetrics and Gynaecology, and Dean, Post-graduate School of Gynaecology and Obstetrics. He

was also Director of the WHO Special Programme of Research in Human Reproduction and Director General of the Italian National Institute of Health.

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<A>Introduction

Until recently, adolescent endometriosis has been considered a rare, often transient, condition not particularly serious for the young patient. Against this background, and not without disagreement by some, we have pointed out that early onset endometriosis (EOE) may at times be severe, necessitating quick diagnosis and proper treatment (Brosens *et al.*, 2013b; 2014). To substantiate this viewpoint, we carefully searched published research, including some early paediatric research, and identified peritoneal reflux from neonatal uterine bleeding (NUB) occurring in 3–5% of female neonates, as a biologically plausible and likely cause of EOE (Brosens and Benagiano, 2013; 2016; Brosens *et al.*, 2013a; Gargett *et al.*, 2014).

At least some forms of adolescent endometriosis, therefore, may represent a subtype of the condition different from adult disease (Brosens *et al.*, 2016) requiring ad-hoc management. A review of recently published research shows that, in the largest study ever published, EOE can be severe and progressive, especially in the form of ovarian endometrioma (Brosens *et al.*, 2013b).

Given this situation, it is important to revisit diagnosis and management of EOE to ensure that, when the condition is suspected, prompt action is taken to prevent, as much as possible, damage to the future reproductive health of the affected adolescent.

Unfortunately, diagnosis is often delayed for years (**Table 1**), even in adult women. In adolescents, in particular, a recent study (Dun *et al.*, 2015) of 25 participants aged 21 years or

less, documented a mean time from the onset of symptoms until diagnosis of 22.8 (\pm 31.0) months (range, 1–132). The median number of physicians who evaluated the adolescents was three (\pm 2.3) (range, 1–12). Clearly, physicians are reluctant to submit an adolescent to traditional laparoscopy. For this reason, we believe that a new, stepwise, minimally invasive approach to EOE is now fully justified.

Correct management must start with proper evaluation of clinical symptoms; these may vary from those seen in adult women (Laufer *et al.*, 2003). Among them, first and foremost, drug-resistant, cyclic or acyclic pelvic pain and dysmenorrhoea. Similarly to what happens for adult women, diagnosis in the adolescent has been based on the combined pillars of laparoscopy and revised American Fertility Society and American Society for Reproductive Medicine classification (American Fertility Society, 1985). Unquestionably, laparoscopy has greatly contributed to our understanding of endometriosis, but the time has come to critically discuss which approach is the most appropriate for the adolescent. This is why the need to revert to laparoscopy for the diagnosis of endometriosis has recently come under scrutiny (Vercellini *et al.*, 2015); today, in the presence of signs of increased risk for EOE, a modern approach calls for use of the new, non-invasive imaging techniques of transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI), which can easily identify the most worrying variant, the ovarian endometrioma.

If imaging gives rise to heightened suspicion, then endoscopic confirmation becomes justifiable and can be carried out using the transvaginal route, on the one hand minimizing invasiveness and, on the other, allowing for immediate treatment.

Here, we present an overview of the pathophysiology and symptomatology of endometriosis in young women, and discuss the most appropriate management, including new options for diagnosis and treatment.

<A>Search strategy

In constructing our opinion, we used *Scopus* and *PubMed* searches for the following terms: endometriosis, endometrioma, endometrial cyst, adolescent, teenager, juvenile, neonatal, dysmenorrhea, pelvic pain, from 1995 until end of 2016. In addition, references and citations from major publications were included in the search.

This material was systematically reviewed in the hope of providing an updated picture of the situation.

<A>The nature of early onset endometriosis

Neonatal menstruation

When dealing with pre-menarcheal and adolescent endometriosis, the starting point must be the classic neonatal autopsy study of Ober and Bernstein (1955). In this study, a spectrum of endometrial progesterone responses in the newborn is described, varying from proliferation to full decidualization and menstrual-like shedding. Full progesterone response was found in only 5% of the neonates, the frequency reported for the occurrence of NUB (Lévy *et al.*, 1964; Kaiser and Grässel, 1974; Huber, 1976; Berić *et al.*, 1985).

The careful histological observations of Ober and Bernstein (1955) made it possible to classify menstrual and neonatal bleedings as ‘progesterone withdrawal bleedings’. It occurs in only a small percentage of neonates; in most, the endometrium at birth possesses an ontogenetic resistance to the action of progesterone and, as a consequence, fails to show decidual transformation. These observations prompted us to develop a new theory on the origin of EOE based on the hypothesis that naïve endometrial progenitor cells can be seeded into the pelvic cavity in concomitance with NUB. These cells, once settled in the pelvic cavity, would stay dormant for years and in the presence of factors known to lead to the development of endometriosis, can be activated at the time of thelarche, resulting in the development of a specific phenotype characterized by more florid and progressive disease because of the presence of highly angiogenic implants, recurrent ectopic bleeding and endometrioma formation (Brosens *et al.*, 2016). This theory is supported by direct evidence that seeded endometrial cells in a neonate can quickly attach themselves to the peritoneum (Arcellana *et al.*, 1997). In addition, using peritoneal explants cultured for 1 h with mechanically dispersed proliferative or secretory endometrium, Witz *et al.* (2001) observed that, in 17 out of 20 explants, the endometrium was adherent to intact mesothelium. In most cases, adhesion to the mesothelium occurred via the endometrial stroma; however, some cases of endometrial epithelium–mesothelium attachment were reported. This study proved that both endometrial cells and stroma can rapidly adhere to the intact peritoneal mesothelium.

This new hypothesis posits that endometrial stem and progenitor cells in NUB may be causally linked to EOE (Brosens *et al.*, 2013a; Gargett *et al.*, 2014). It offers an explanation for both the occurrence of endometriosis in the pre-menarcheal girl and the presence of severe endometriosis, including ovarian endometriomas, in adolescents. In particular, we have proposed a ‘physiologic

pathway' for the formation of endometriotic implants (Brosens and Benagiano, 2017). In addition, we have suggested ways to validly collect data in cross-sectional and case-control studies (Puttemans *et al.*, 2017).

Clinical presentation

Marsh and Laufer (2005) described endometriosis as the cause of chronic pelvic pain in five premenarcheal girls without an obstructive reproductive tract anomaly. At laparoscopy, multiple clear and red lesions consistent with peritoneal endometriosis were identified and ablated. Six and 8 years later, two girls had a repeat laparoscopy documenting the reappearance of typical lesions. Subsequently, premenarcheal endometriosis with an ovarian endometrioma or subtle endometriosis was described in an 11-year-old premenarcheal girl (Gogacz *et al.*, 2012) and a 9-year-old girl (Ebert *et al.*, 2009).

It has been estimated that the younger the girls at the time of diagnosis, the more severe the stage and size of the lesions (Emmert and Riedel, 1998), and that pelvic abnormalities, such as endometriosis, or uterine anomalies might be found in about 10% of adolescents with severe dysmenorrhoeal symptoms (Harel, 2008). Adolescents with chronic pelvic pain not responding to medical treatment were found to have a high rate of stage I or II endometriosis (Laufer *et al.*, 1997). A recent review based on 15 selected studies in adolescent girls undergoing laparoscopic investigation, found an overall prevalence of visually confirmed disease of 62%, rising to 75% in the presence of chronic pelvic pain refractory to treatment; of 70% with dysmenorrhea and 49% with chronic pelvic pain not necessarily refractory to treatment (Janssen *et al.*, 2013).

Dysmenorrhoea is a serious problem in adolescence, causing, among others, absenteeism from school or work (Treloar *et al.*, 2010; Chapron *et al.*, 2011a; Zannoni *et al.*, 2014). Of practical

importance is the observation that it seems possible to predict an increased risk of endometriosis in girls with early onset dysmenorrhoea (Chapron *et al.*, 2011b).

In clinical practice, however, the delay in diagnosis remains a critical issue; particularly in view of the observation that the earlier dysmenorrhoea appears, the longer the delay in diagnosis (Ballweg, 2004; Hudelist *et al.*, 2012). In a recent cohort of 25 young women (≤ 21 years), the most common complaints were dysmenorrhoea (64%), menorrhagia (44%), abnormal or irregular uterine bleeding (60%), gastrointestinal symptoms (56%) and genitourinary symptoms (52%) (Staal *et al.*, 2016).

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The diagnostic delay, together with the different origin, can explain the severity of endometriosis affecting some adolescents, especially the form affecting the ovaries (Yang *et al.*, 2012; Brosens *et al.*, 2013; Smorgick *et al.*, 2014; Audebert *et al.*, 2015). For this reason, finding a simple, non-invasive tool for screening the presence of endometriosis in adolescents is mandatory.

<A>The phenotype of adolescent endometriosis

In our opinion, even if endometriosis in an adolescent originates from the activation of dormant stem or progenitor cells seeded below the peritoneum through neonatal menstrual reflux, its development follows the same path and requires the presence of the same facilitating factors necessary for the development of any other form of endometriosis. At the same time, we have stressed that EOE can become a hidden, debilitating and progressive disease that deserves full attention to preserve the integrity of the adolescent's reproductive life (Brosens *et al.*, 2013b; 2014). The differences between early onset and adult endometriosis are presented in **Table 2**.

Progression

There is wide agreement that it is close to impossible to predict in which cases the disease will progress; however, given the present delay in diagnosis, when symptoms persist for years, there is a clear possibility that the disease is progressing.

In a recently published cohort of 500 women, correlation between stage of endometriosis and age was found to be small ($r = -0.04$; 95% CI, -0.13 to 0.04 ; $n = 471$). At the same time, a literature search identified 16 studies on adults with follow-up ($n = 162$) where laparoscopically proven progression occurred in 31% of the cases ($n = 162$) (Savaris *et al.*, 2014). Also Saridogan (2016) reviewing available evidence concluded that EOE can be progressive in a significant proportion of cases.

In adolescents, especially worrying is ovarian endometriosis, caused by invagination of ovarian cortex, with or without adhesion to the posterior leaf of the parametrium (Hughesdon, 1957). Inspection of the pseudo-cyst allows distinguishing between the endometrioma with a red, highly vascularized mucosal lining and the black endometrioma with a dark, pigmented fibrotic tissue (Brosens *et al.*, 1994). If the fibrosis of inner cortex and devascularization progress, they can also progressively affect follicle reserve (Katajima *et al.*, 2011).

Data available up to 2013 indicate that, out of a total of 403 reported cases, by the age of 20 years or younger, 147 (or 36%) were revised American Fertility Society stage III or IV, although severity greatly differed among studies (**Table 3**). Indeed, the largest of these investigations (66 cases <20 years, not using the revised American Fertility Society classification), found stage III and IV in 4% of the adolescents (Goldstein *et al.*, 1980), whereas the second largest, a cohort of

63 cases (≤ 20 years) (Yang *et al.*, 2012), observed stage I or II disease in only 11% of their patients, with 89% being at stage III or IV. They made an interesting observation: western reports generally indicate less severe disease than Chinese reports. A possible explanation may be that, in the Chinese series, cases with congenital anomalies that may cause menstrual reflux were reported, substantially increasing the likelihood of peritoneal seeding with endometrial cells.

Indirect, but strong evidence, however, exists of a tendency of the disease to progress and produce early damage (Brosens *et al.*, 2013b). More recent studies confirm the potential severity of EOE. In a retrospective cohort of 86 adolescents or young women (≤ 22 years), Smorgick *et al.* (2014), found stage I or II disease in 66 (76%) and stage III or IV in 20 (23%). The pathology with advanced stages included ovarian endometriomas in 14, rectovaginal nodules in one and diaphragmatic and pulmonary endometriosis in one case. Women with advanced stage were slightly older at the time of diagnosis, suggesting that adolescent endometriosis may be a progressive disease when affecting the ovaries. In the study published by Dun *et al.* (2015), 68% of adolescents with laparoscopically confirmed diagnosis had stage I, 20% stage II, and 12% stage III disease. Atypical endometriosis lesions were most commonly observed during laparoscopy. Finally, Audebert *et al.* (2015) reported on a retrospective cohort involving 55 adolescents aged 12–19 years (mean age 17.8 years). Superficial implants were encountered in 31 cases (56%), endometriomas in 18 (33%), and deep infiltrating endometriosis in six (11%). Sixty per cent of patients were scored as stages I to II and 40% as stages III to IV.

If we accept the theory of repeated tissue injury and repair (Guo *et al.*, 2015; Zhang *et al.* 2016b), then endometriotic lesions normally undergo progressive epithelial–mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, smooth muscle metaplasia and fibrogenesis. In

other words, endometriosis normally progresses if not intervened, and, ultimately to fibrosis. This theory has been demonstrated to be true for baboon and mouse models of endometriosis (Zhang *et al.* 2016c; 2017). In other words, that endometrisis is a progressive disease is at least theoretically plausible, owing simply to the very nature of endometriotic lesions which undergo cyclic bleeding (Brosens, 1997).

Recurrence

In reviewing published data up to 2009, Guo (2009) reported a high overall recurrence rate for adult disease, estimated as 21.5% at 2 and 40–50% at 5 years. He was forced, however, to conclude that reported risk factors for recurrence were often conflicting.

In an investigation specifically aimed at adolescents, Tandoi *et al.* (2011) followed 57 women aged 21 years or younger over a 5-year period and in 32 (56%) observed a recurrence of the disease after surgery. Its rate increased with time from surgery, with no apparent association with site or stage of the disease, type of surgery, and post-surgical medical treatment. Recurrence was proven by a second laparoscopy in 11 cases (34%), whereas, in the remaining 21 cases (66%), it was assumed because of the reappearance of symptoms or through clinical or sonographic findings.

The following year, Yang *et al.* (2012) published data on recurrence in 35 adolescents. Mean follow-up was 46.3 months (range 12–98 years); recurrence was defined as appearance of ‘new pelvic endometriosis and/or masses which was found by ultrasound or similar symptoms which recurred at least six months post-operatively’. Recurrence was observed in 45.7% of the 35 cases (including three with genital malformations), with an average recurrence time of 33.4 months.

Recurrence, however, occurred in 60% of 15 adolescents not treated postoperatively; in 46% of 13 who received an oral contraceptive medication; in one of the two patients given a progestin and in none of the five treated with a gonadotrophin releasing (GnRH) analogue. The difference between patients treated with GnRH analogue and those who are not was statistically significant ($P = 0.038$).

In the above-mentioned study published by Audebert *et al.* (2015), 17 out of the 50 adolescents not lost to follow-up (34%) underwent a repeat laparoscopy because of persisting pain. Among the adolescents followed up, 12 had endometriomas and 12 had deep endometriosis; the observed recurrence rates were 37% and 50%, respectively.

Young age seems to be a major risk factor for recurrence of ovarian endometriomas after cystectomy, risk being inversely related to the age at surgery. Kikuchi *et al.*, (2006) evaluated recurrence after laparoscopic cystectomy of 417 endometriomas using transvaginal ultrasonography over a mean period of 21.4 ± 16.8 months. During this period, 15.9% of the patients experienced recurrence with a cumulative recurrence rate per patient of 31.7% over 60 months and age at surgery was inversely correlated with recurrence. Sengoku *et al.* (2013) carried out a retrospective evaluation of 248 women with endometriomas, with a minimum of 2 years follow-up after laparoscopic excision, and found that the only identifiable risk factor was a younger age at surgery. Ouchi *et al.* (2014) retrospectively reviewed the records of 167 patients who underwent laparoscopic excision of ovarian endometriomas and were followed-up for 1–10 years. They assessed potential risk factors for recurrence in patients receiving no medication and, again found that age at surgery was the only significant risk factor for recurrence.

When evaluating these results a word of caution is mandatory, as patients with appropriate follow-up usually represent a selected group and may well not be representative of the general population.

Prevalence of ovarian involvement

Ovarian endometriomas were often not identified unless they were present as large ovarian cysts. One such large endometrioma was diagnosed in a pre-menarcheal girl (Gogacz *et al.*, 2012). The use of imaging techniques has made it possible to diagnose increasing numbers of ovarian endometriomas with adhesions. In terms of severity, this has been evaluated according to the revised American Fertility Society classification system; unfortunately, staging with this classification may not reflect the pathology of pelvic organs involved, such as the ovaries.

The cohort published by Smorgick *et al.* (2014) included 14 cases of ovarian endometriomas (**Table 4**). In the series of 63 cases reported by Yang *et al.* (2012), the ovary was affected in 55 cases (87.3%); this percentage rose to 93% (14 out of 15) in the presence of genital tract anomalies.

By comparing clinical features of the endometrioma in adolescents to those of older age groups, Lee *et al.* (2013) found that adolescents experienced menarche at a significantly earlier age and that the main symptom was pain.

According to the European Society of Human Reproduction and Embryology guidelines, the minimum diameter to warrant intervention is 3 cm; however, this has been arbitrarily chosen on the assumption that, below that size, an image may represent a dysfunctional haemorrhagic cyst

(Dunselman *et al.*, 2014). Furthermore, current guidelines are based largely on observations in the adult and do not reflect the real situation in adolescent and young women. Consequently, the rationale for investigating other factors besides dysmenorrhoea that may be linked with an increased risk of EOE resides in the poor value of existing signs.

<A>The search for signs and symptoms

Recently, Zannoni *et al.* (2016) suggested five practical ways to diagnose endometriosis as early as possible and detect patients at risk of developing the disease in the future: never underestimate the pain; always consider endometriosis as a possible cause of severe cyclic pain; obtain a detailed and accurate history before performing clinical evaluation and pelvic sonography; treat the pain with hormonal therapies and analgesics; plan frequent follow-up visits to re-evaluate the patient. Although these recommendations have value, more is required to speed up diagnosis, including indirectly detecting an increased risk of NUB.

Clinical conditions linked to an increased risk of neonatal uterine bleeding

We have already reviewed a number of factors capable of increasing the occurrence of NUB and the likelihood of an association of these factors with the presence of EOE during adolescence (Brosens and Benagiano, 2015). For this reason, they will be briefly summarized here.

<C>Low birth weight and preeclampsia

In the clinical series by Lévy *et al.* (1964), low birth weight was reported to be a major cause of NUB, although no distinction was made between prematurity and small for gestational age.

Another important association with NUB was the presence of preeclampsia. The risk rose to 32% for mild preeclampsia and to 46% for the severe form.

<C>Post-maturity

In the study by Lévy *et al.* (1964), risk of NUB in post-maturity was also elevated, although not significantly. In the cohort study by Berić *et al.* (1985), 126 infants were premature, 2241 at term and 110 post-mature. The incidence of NUB was 0.78%, 3.79% and 9.10%, respectively, confirming that post-maturity is a significant cause of NUB.

<C>Feto-maternal incompatibility

Lévy *et al.* (1964) found an increased risk of NUB in association with ABO or Rhesus blood group incompatibility at term. The risk was highly significant.

Epidemiological links

Several epidemiological studies have explored links between in-utero events and risk of endometriosis.

Missmer *et al.* (2004) documented an increased risk of endometriosis for lower birth weight with a relative risk of 1.2 (95% CI 1.0 to 1.8; $P < 0.01$). In the Nurses' Health Study II with a 10-year follow-up, after adjusting for age, calendar time, parity, race and body mass index at age 18 years, a linear increase was observed in the incidence rate of endometriosis with decreasing birthweight (RR 1.3 for birthweight < 5.5 pounds versus 7.0–8.4 pounds, 95% CI 1.0 to 1.8, $P < 0.01$). Premature delivery was not associated with an increased risk of endometriosis (Vitonis *et al.*, 2010). A case-control study by Borghese *et al.* (2015) of women operated for benign

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gynaecologic conditions included 358 patients with histologically proven endometriosis and a control group of 375 patients without endometriosis as surgically checked. Patients with birth weight 2500 g or less had a higher risk of endometriosis. A 'dose-response effect' was observed for the risk according to birth weight and also an increased risk of developing deep infiltrating endometriosis. In contradistinction to this, in another smaller case-control study of 91 women with endometriosis and 82 controls, Somigliana *et al.* (2011) failed to detect any association with prematurity or birthweight. Wolff *et al.* (2013) conducted a matched cohort study involving 473 women undergoing laparoscopy and laparotomy, and a matched population cohort comprising 127 women undergoing pelvic MRI. They found that in-utero exposures were not statistically associated with the odds of an endometriosis diagnosis. Reduced odds, however, were observed for preterm birth (OR = 0.41; 95% CI 0.18 to 0.94). The observation that preterm birth reduces risk of endometriosis, together with the finding of low bleeding frequency in preterm newborns (Huber, 1976), support the hypothesis of NUB as a potential cause of EOE.

<A>Progress in management

Imaging techniques

Even with the advent of new, minimally invasive diagnostic techniques, a need remains, especially when dealing with adolescents, for non-invasive methods offering an accurate diagnosis of the presence, type, location and extent of endometriotic lesions. Two techniques are today the most frequently used: TVS and MRI. Both can identify and characterize severe endometriotic lesions, but unfortunately, virtually no information is available on their application in adolescents.

The use and applications of sonography and MRI to the diagnosis of endometriosis have been recently reviewed, concluding that both have proved to be particularly sensitive in the diagnosis of endometriosis (Saba *et al.*, 2015; Exacoustos *et al.*, 2017).

To determine progression of disease through interstitial fibrosis and microvascular injuries associated with ovarian endometriotic cysts, Qiu *et al.* (2013) used transvaginal colour Doppler sonography and evaluated ovarian interstitial blood flow, finding that changes in resistance indices in ovaries with endometriosis were related to interstitial fibrosis and devascularization. The issue is complex and recently Kelleher and Goldstein (2015) pointed out that, to carry out a proper differential diagnosis for adnexal masses in childhood, the paediatrician needs to broadly know the wide range of adnexal pathology. A correct diagnosis requires consideration of the patient's age, presenting complaints, physical examination findings, and imaging results; only after careful evaluation of these variables does it become feasible to generate a list of possible diagnoses and an appropriate treatment plan.

****Medical treatment

In a document prepared under the auspices of the World Endometriosis Society (Johnson and Hummelshoj, 2014), the consensus was that, in dealing with EOE, both medical and surgical modalities have the potential of improving quality of life, alleviating symptoms, preventing the development of more severe disease later in life and minimizing the likelihood that future fertility may become compromised.

Although surgery is effective in treating endometriosis in adults, it may well be a double-edged sword in adolescents. Aside from the increase in risk of premature ovarian failure caused by

surgical treatment of ovarian endometriomas (Seyhan *et al.*, 2013), recent animal and epidemiological studies indicate that surgery, in and by itself, may promote the development of endometriosis (Long *et al.*, 2016; Liu *et al.*, 2016; Zhang *et al.*, 2016a; 2016c). In fact, a history of surgery for endometriosis is correlated with the presence and severity of deep infiltrating endometriosis, underlining the necessity of a thorough preoperative assessment and the need for providing complete information to these patients before undertaking further surgery (Sibiude *et al.*, 2014). This is why medical treatments assume a special importance in treating adolescents.

In principle, the same drugs can be used in adolescent and adult patients. The critical issue, however, is the mentioned progressive and dynamic nature of endometriosis, shown both in spontaneous and induced disease (D'Hooghe *et al.*, 1996; Harirchian *et al.*, 2012; Zhang *et al.*, 2016a, 2016b; 2016c).

In a mini review of dysmenorrhoea in adolescence, Harel (2006) states: 'If dysmenorrhea does not improve within 6 months of treatment with non-steroidal anti-inflammatory drugs (NSAID) and oral contraceptive pill, a laparoscopy is indicated to look for endometriosis'. Once diagnosis is posed, Unger and Laufer (2011) have proposed a combined medical–surgical approach as the best method to slow its progression. This, together with no delay in treatment, seem key to the disease's successful containment. At any rate, an attempt with a medical regimen should represent the first choice.

Oestrogen–progestin combinations have been empirically used in treating young patients with suspected or confirmed endometriosis, sometimes with good results. Also, progestins alone have been used in the past, including norethisterone acetate (15 mg/day), oral (30–50 mg/day) and

depot (150 mg every 3 months as an injection) medroxyprogesterone acetate (Propst and Laufer, 1999; Laufer *et al.*, 2003). More recently, one compound that seems to have yielded good results without appreciable untoward effects in women aged between 18 and 52 years of age is dienogest (Schindler *et al.*, 2010). The conventional dose is at present 2 mg daily.

Doctors have been reluctant to use GnRH analogues, especially in young patients, because of secondary hypo-oestrogenic side-effects; however, the so-called ‘add-back’ therapy may be a means to overcome this problem. Indeed, progestins, with or without the addition of a low-oestrogen regimen, may allow an effective extension of GnRH analogue therapy (Surrey, 2010).

Stepwise minimally invasive approach

Vercellini *et al.* (1989) assessed the value of diagnostic laparoscopy in the differential diagnosis of chronic pelvic pain in 47 adolescents aged 11–19 years. No pelvic abnormalities were detected in 19 patients (40.4%), endometriosis was detected in 18 (38.3%), partially obstructive genital tract malformations in four (8.4%), and other types of pathology in six (12.8%). Nearly 60% of the patients had a treatable pelvic disease, leading to the conclusion that diagnostic laparoscopy is an invaluable tool in the diagnosis of chronic pelvic pain in adolescents and should be carried out before prescribing long-term medical treatment or starting a psychiatric evaluation. Weighing the evidence, in the presence of an endometrioma, it seems that, in principle, treatment in an early stage is recommendable as it carries less risk for ovarian damage with loss of follicle reserve.

According to the European Society of Human Reproduction and Embryology guidelines for the diagnosis and treatment of endometriosis, under the section on ‘endometriosis in adolescents’ (ESHRE, 2016): ‘Laparoscopy should be considered if adolescents with chronic pelvic pain who

do not respond to medical treatment (NSAID and oral contraceptive pills) since endometriosis is very common under these circumstances'. Nonetheless, adolescents may not appreciate the abdominal scars of a diagnostic procedure. In 1998, Gordts *et al.* (1998) described 'transvaginal hydro-laparoscopy' an endoscopic needle technique, and in the same year Watrelot (1998) described a similar office procedure. Both techniques make use of saline for the pelvic distension, and are specifically recommended for surgery of ovarian endometriomas. Transvaginal hydro-laparoscopy has several advantages for surgery of endometriomas with a size up to 20 mm (**Figure 1**) (Darwish *et al.*, 2000; Brosens *et al.*, 2001; 2007).

A multinational retrospective investigation of the risk and outcome of complications in a series of 3667 cases showed that bowel lesions tended to be minor and under strict conditions could be treated expectantly (Gordts *et al.*, 2001).

In summary, we propose a stepwise minimally invasive approach to the diagnosis and treatment of adolescent endometriosis, as outlined in **Figure 2**. This consists of the following steps:

<C>Taking the patient's history

Ask for factors contributing to a possible higher risk of presence of endometriosis (like presence of neonatal uterine bleeding); for events leading to utero placental ischemia (low birth weight, pre-eclampsia, post maturity and ABO incompatibility); and for time of onset of menstruation and cycle length.

<C>Clinical examination

Exclude uterine anomalies or pathology of the pouch of Douglas.

<C>Imaging evaluation

Carry out a transvaginal or abdominal (in case of a non-sexually active adolescent), ultrasound imaging.

<C>Management

If ultrasound is negative, medical treatment with NSAID, progestins, or hormonal contraception should be started. When symptoms are eliminated or substantially improved with this medication, regular follow-up every 6–12 months is recommended. If pain is resistant to the medication, presence of endometriosis should be excluded by performing a magnetic resonance imaging, following which transvaginal or standard laparoscopy should be considered.

If ultrasound findings are positive, further management is determined by severity of the pathology. In the case of a small unilateral endometriotic cyst, hormonal medication and NSAID can be started with a further control every 6–12 months. In case of persistent pain, patients should be referred for an MRI or directly for an operative transvaginal hydro-laparoscopy (≤ 20 mm) or laparoscopy (> 20 mm in diameter).

In case of severe findings at ultrasound, and certainly if endometriomas are bilateral, patients should be referred to experienced surgeons for surgery after comprehensive information is provided and consent obtained. As surgery has the potential of impairing ovarian reserve, and as recurrence rates after surgery in young adolescents are high, patients should be offered the possibility of cryopreservation of ovarian tissue to preserve their fertility.

Outcome of surgery

In a small study of 20 adolescents, Yeung *et al.* (2011) suggested that, in the hands of a skilled laparoscopist, complete excision of all areas of abnormal peritoneum with typical and atypical endometriosis may be sufficient to eradicate the disease. They investigated long-term outcomes up to 66 months (on the average 23.1 months) of patients who were not specifically advised to take postoperative hormonal suppression. Although the rate of repeat surgery was 47.1%, the rate of recurrent endometriosis at surgery was zero. Rimbach *et al.* (2013) agreed with this surgical strategy, but warned that the possibility of achieving this goal is limited by the difficulty of detecting all foci and the risks associated with radical surgical strategies.

These results were partly confirmed by later investigations. In the study by Dun *et al.* (2015), mean age at the time of surgery was 17.2 (± 2.4) years (range, 10–21), and patients were followed up for 1 year. At 1 year, 64% reported resolved pain, 16% improved pain, 12% continued pain, and 8% recurrent pain. The authors concluded that once the disease is diagnosed and treated by an experienced gynaecologist, these patients have favourable outcomes with hormonal and non-hormonal follow-up treatment. Audebert *et al.* (2015) in their study of 55 cases concluded that adolescent endometriosis is not a rare condition and that the effect on subsequent fertility seemed to be limited. Among patients treated for deep infiltrating endometriosis, a trend was observed for higher rates of recurrence that required repeat laparoscopy.

Combined surgical and medical approach

In their review of treatment options for adolescent endometriosis, Laufer *et al.*, (2003), state that the goal of medical treatment is twofold: treat pain that may subsist in the event of suboptimal ablation and slow the progression of the disease.

It, therefore, seems that proper treatment of adolescents should consist of prescribing medication after minimally invasive surgery. In this context, a study involving a series of 194 adolescents and young adult women showed that the postoperative administration of norethisterone acetate is an effective option to manage pain and bleeding for all stages of endometriosis (Kaser *et al.*, 2012).

New options

There is palpable disappointment over the slow progress in the development of novel therapeutic agents, and few new drugs have been approved in the last decade for treating endometriosis (Vercellini *et al.*, 2011).

At the same time, several experimental drugs have undergone preliminary evaluations, and seem to show promising results.

One option is to use dopamine receptor agonists (DRA), compounds capable of activating signalling pathways leading to changes in gene transcription (Novella Maestre *et al.*, 2009; Delgado-Rosas *et al.*, 2011). In a small clinical study, administration of DRA quinagolide in patients with hyperprolactinaemia, led to the reduction of peritoneal endometriotic lesions in two-thirds of cases, and elimination in the residual one-third (Gómez *et al.*, 2011). Histologically, degeneration was supported by down-regulation of vascular endothelial growth factor (VEGF) and its receptor-2 (VEGFR2), of three proangiogenic cytokines and of the plasminogen activator inhibitor-1 (PAI-1). In this study, DRAs reduced inflammation, interfered with angiogenesis and enhanced fibrinolysis.

Indeed, numerous compounds are capable of exerting anti-angiogenic effects on endometriotic lesions *in vitro* and *in vivo*, including progestins, danazol and GnRH agonists, although no convincing clinical evidence has been reported for their efficacy. Results with antiangiogenic agents have been summarized by Laschke and Menger (2012). As endometrium also undergoes cyclic physiological angiogenesis, it is unclear how angiogenesis can be targeted without causing untoward collateral damage.

Another possible option is the inhibition of histone deacetylase through the administration of valproic acid (Li *et al.*, 2014), a prescription drug approved for treating epilepsy and bipolar disorders. Extensive preclinical studies indicate that this compound holds promise (Guo, 2009b) and two clinical studies have shown that valproic acid is effective in treating symptomatic and drug-refractory adenomyosis (Liu *et al.*, 2008; 2010).

For both DRAs and valproic acid, no large clinical trial has ever been conducted. Given that these are old drugs and their patents have long expired, it is unlikely that any large-scale clinical trial would be launched soon.

<A>Long-term concerns

Both medical and surgical management can give rise to long-term concern, although firm data are still lacking.

Adolescent girls and young women are near or at the end of their developmental stage, and ready to realize their reproductive potential. As most, if not all, drugs are hormonal, some concerns have been raised about their long-term effects, given that many tissues and organs express

oestrogen and progesterone receptors. In female rodents, oestradiol and progesterone are known to regulate sexual behaviours, ranging from the willingness to mate, soliciting interest from the male partner and leading to successful copulation (Erskine, 1989; Pfau *et al.*, 1999; Sakuma, 2008). With a large dose of oestradiol, repeated oestradiol priming, or both, the female rodent's proceptivity can occur even without progesterone priming (Parsons *et al.*, 1984; Pfaff *et al.*, 2002; Micevych *et al.*, 2008; Jones *et al.*, 2013; Uphouse *et al.*, 2014;). Even allowing for substantial differences in humans, any hypo-oestrogenic environment resulting from medical treatment, may, in theory, give rise to long-term consequences, well beyond those on bone mineral content.

Concerns have also been raised about the surgical approach. The main concern is that the current two options of cyst excision or expectant management both have potential deleterious effects on the ovarian follicle reserve. For this reason early diagnosis and pathology-based surgery of the endometrioma may be the missing link in current surgical approach (Gordts *et al.*, 2015).

<A>Conclusion

The purpose of this review was to critically re-evaluate present management of early onset endometriosis, starting with its possible different origin than the adult form and new knowledge of its symptomatology and pathogenesis, continuing with a search for new, simple, non-invasive markers of an increased risk, and ending with reappraisal of usefulness of new imaging screening techniques.

When dealing with extra-ovarian endometriosis, a major issue relates to an almost inevitable delay in its diagnosis. This is due, on the one hand, to often non-specific symptoms in adolescence and, on the other, to the reluctance of gynaecologists to use presently available invasive diagnostic procedures. For this reason, a wider application in adolescence of the new, non-invasive techniques of transvaginal ultrasound and MRI to identify the presence of all forms of endometriosis is mandatory.

Diagnosis of mild forms of endometriosis in teenagers by transvaginal ultrasound remains confined to relatively few, ad hoc-trained specialists; various techniques of MRI seem capable of identifying the presence of endometriosis in its various forms, in most young patients.

We propose that, in the presence of pelvic pain, dysmenorrhoea and an ovarian cystic structure visible at transvaginal ultrasound or MRI, feto-maternal factors increasing the risk of neonatal uterine bleeding can be used to focus on higher-risk cases, e.g. women with endometriosis of neonatal origin. This will shorten the current delay in time to diagnosis. Indeed, feto-maternal factors, including preeclampsia and fetal growth restriction, have in common the presence of utero-placental disorders with reduced blood supply to the placenta, whereas the history of feto-maternal incompatibility may indicate the presence of chronic fetal anaemia. All these conditions cause hypoxia and fetal distress during the last months of pregnancy. The identification of disorders associated with utero-placental ischaemia, such as preeclampsia and fetal growth restriction, should be used to allow a potential distinction between endometriosis of neonatal versus adult origin. All this, however, can only be achieved through properly designed prospective studies.

Early diagnosis is of paramount importance for ovarian endometriomas, as, in young patients this form has a tendency to progress, endangering their reproductive potential.

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Declaration

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Figure legends

Figure 1: Transvaginal hydro laparoscopy for reconstructive surgery of non-fibrotic ovarian endometrioma up to 3 cm in diameter. (A) Disconnection of adhesions between ovary and pelvic side wall at the site of invagination; (B) ovariolysis and exploration of what lies beneath the surface with sharp micro scissors; (C) the ‘chocolate’ content appears, clearly indicating the presence of an underlying endometrioma; (D) the endometrioma is further incised with the use of a bipolar needle to an opening of approximately 15 mm in diameter. Image taken after washing out the chocolate content; (E and F) inside view, clearly showing the presence of red cobblestone-like ectopic endometrium, well differentiated at pathology (red arrows) and concentrated mostly behind the site of invagination and retraction. With a 5 Fr biopsy forceps, biopsies can easily be taken under direct visual control; (G) endometriotic implants (blue arrows) inside the endometrioma superficially spread on a white background of inverted ovarian cortex; (H and I) end result of a conservative ‘minimally invasive’ ablative surgery with a 5 Fr bipolar probe or a 1000 μ fibre of a 15W diode laser under direct visual control, minimizing the damage to the cortex, i.e. preserving ovarian reserve to a maximal extent.

Figure 2: Stepwise minimally invasive approach to the diagnosis and treatment of adolescent endometriosis. MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory. TLH, total laparoscopic hysterectomy.

Comment [MD6]: Author: should THL in Figure 2 be TLH (total laparoscopic hysterectomy?) Please delete changes and amend if incorrect.

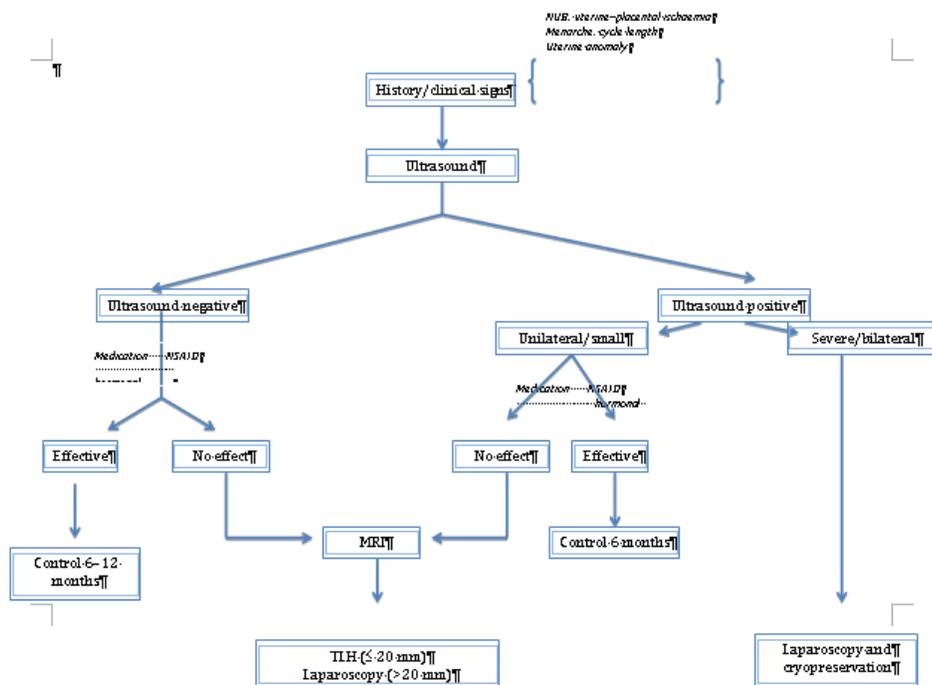


Table 1. Delay of diagnosis of endometriosis.

<i>Reference (years)</i>	<i>n</i>	<i>Country</i>	<i>mean ± SD</i>
Hadfield <i>et al.</i> , 1996	218	UK USA	8.0 ± 7.92 11.7 ± 9.05
Arruda <i>et al.</i> , 2003	200	Brazil	7.0 ^a (3.5–12.1) ^b
Ballweg, 2003	4000	USA	9.3
Husby <i>et al.</i> , 2003	400	Norway	6.7 ± 6.2
Hudelist <i>et al.</i> , 2012	171	Austria/Germany	10.4 ± 7.9
Staal <i>et al.</i> , 2016	139	Netherlands	7.4 ^a
Dun <i>et al.</i> , 2015	25 ^c months	USA	22.8 ± 31.0 (1–132) ^b

^aMedia.^bRange.^cAdolescents aged 21 years or younger.

Table 2. Phenotype of adolescent versus adult endometriosis.

<i>Adolescent endometriosis</i>	<i>Adult endometriosis</i>
Symptoms Severe primary dysmenorrhoea Frequently resistant to oral contraceptive pill and non- steroidal anti-inflammatory drugs	Symptoms Moderate dysmenorrhoea
Peritoneal Red, clear or vesicular implants Minimal fibrosis Ovarian endometrioma Cortex Angiogenic adhesions Stigma of inversion with implant Invaginated cortex Marble white Thin angiogenic mucosal lining Medulla Stretched Deep endometriosis Seldom	Peritoneal Black intraperitoneal implants White, fibrotic Ovarian endometrioma Cortex Dense adhesions Stigma of inversion with implant Invaginated cortex Dark pigmented Endometrial tufts Thickened by fibrosis Medulla Smooth muscle metaplasia Fibrosis and devascularization Deep endometriosis Adenomyoma Microendometrioma
Concomitant pathology Obstructive genital tract anomalies	Concomitant pathology Rectal and bladder endometriosis

	Uterine adenomyosis
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Based on Hughesdon (1957), Janssen *et al.* (2013) and Brosens *et al.* (2013b).

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Table 3. Staging of endometriosis according to revised American Fertility Society/American Society for Reproductive Medicine classification in adolescents.^a

	Age range	Cases (n)	GTA (%)	I (%)	II (%)	III (%)	IV (%)	Ovarian endometrioma (%)
Vercellini <i>et al.</i> (1989)	10–19	18	NM	67	33	0	0	NM
Davis <i>et al.</i> (1993)	13–20	36	0	50 ^b		50 ^c		19
Reese <i>et al.</i> (1997)	11–19	49	NM	80	12	6	2	NM
Laufer <i>et al.</i> (1997)	13–21	31	0	77	23	0	0	0
Bai <i>et al.</i> (2002)	14–21	39	NM	10	44	28	18	NM
Ventolini <i>et al.</i> (2005)	12–18	52	0	14	39	43	4	0
Stavroulis <i>et al.</i> (2006)	13–20	11	0	45 ^b		55 ^c		0
Vicino <i>et al.</i> (2010)	15–21	38	0	18	13	34	34	3
Roman <i>et al.</i> (2010)	14–20	20	NM	40	45	5	10	NM
Yang <i>et al.</i> (2012)	12–20	63 ^e	24	8	3	52	37	87
Smorgick <i>et al.</i> (2014)	<22 ^d	86	0	67	9	8	15	16
Dun <i>et al.</i> (2015)	<21	25	NM	68	20	12	0	0
Audebert <i>et al.</i> (2015)	12–19	55	4	60 ^b		40 ^c		33

^aAdapted and completed from Brosens *et al.* (2013b).

^bStages I and II.

^cStages III and IV.

^dAge of revised-American Fertility Society group I and II versus III and IV, respectively: 18.7 ± 2.2 years and 20.4 ± 1.4 ($P < 0.001$).

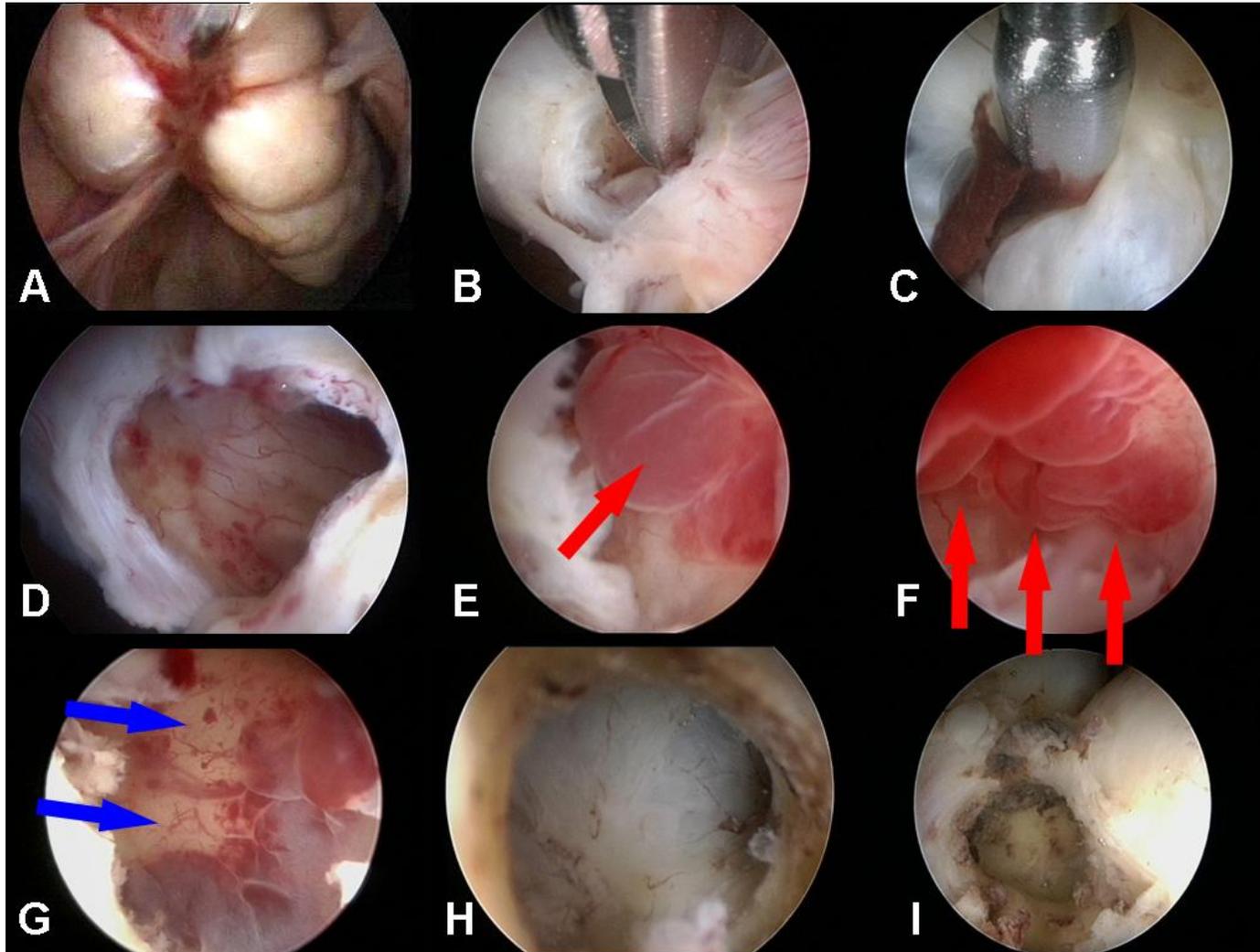
^eOf all the 15 cases with anomalies, ovaries were involved in 14 (93%), whereas rectivaginal pouch and uterosacral ligaments were only involved in two cases (13%). Of the 48 cases without anomalies, however, 26 had rectivaginal pouch or uterosacral ligaments involved (26/78).

GTA, genital tract anomaly; NM, not mentioned.

Table 4. Comparison of findings in two recent large cohorts of adolescents with proven endometriosis.

	<i>Smorgick et al., 2013</i>	<i>Yang et al., 2012</i> <i>All cases</i>	<i>GTM</i>
<i>Age (years)</i>	≤ 22	≤ 20	
Total number of cases	86	63	15
Stage I or II	66	7	0
Stage III or IV	20	56	15
Ovarian, n (%)	14 (70)	55 (98)	14 (93)
Rectovaginal or uterosacral, n (%)	2 (10)	38 (68)	2 (13)
Severe adhesive, n (%)	4 (20)		

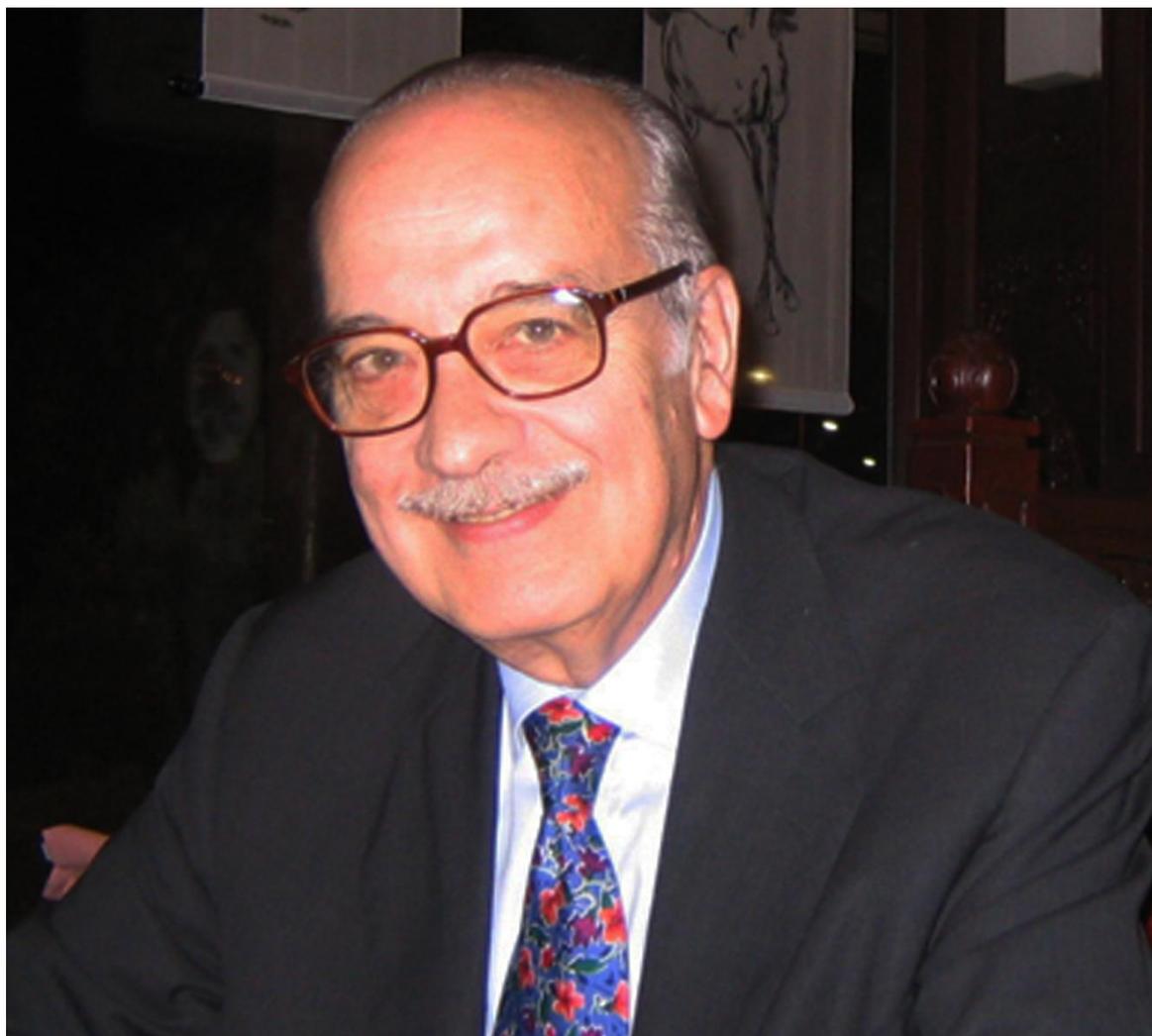
 GTM, genital tract malformation.



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Figure 1.jpg

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