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Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion

I. Brosens[1,*], S. Gordts[1], and G. Benagiano[2]

[1]Leuven Institute for Fertility and Embryology, Leuven, Belgium [2]Department of Gynaecology, Obstetrics and Urology, Sapienza University, Rome, Italy

*Correspondence address. Leuven Institute for Fertility and Embryology, Leuven, Belgium. E-mail: Ivo.brosens@med.kuleuven.be

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ABSTRACT: Endometriosis in the adolescent has, in recent years, been discovered to be a challenging problem in gynaecology. Although the pain may start at a young age, even before the onset of menstruation, the diagnosis by laparoscopy is almost always postponed for several years, by which time destructive lesions have affected the tubo-ovarian structures and severely compromised fecundability. Several factors may play a role, but one important reason for this disease progression is likely to be the delay in diagnosis. Therefore, transvaginal ultrasounds and transvaginal access with a less invasive needle endoscopy are recommended for exploration of the pelvis, diagnosis of endometriosis and treatment at an early stage before severe lesions develop.

Key words: endometriosis / adolescence / adult / pathogenesis / laparoscopy

Background

The presence of endometriosis in the adolescent young woman seems similar to a Mona Lisa smile with a mysterious innocence. The complaints are common and elicit compassion, but do not stimulate a search of the cause. The clinical reality is that common complaints of dysmenorrhoea or acyclic pelvic pain may cover a disease with a severity that is not reflected by the degree of discomfort and may have already reached a stage where the future reproductive life of an otherwise healthy teenager is severely compromised. After a century of intensive research, endometriosis remains a disease with a delayed diagnosis, mainly because non-invasive tools are not available for early stage diagnosis of the condition. This paper intends to review systematically major studies on adolescent endometriosis published since 1979 when the American Fertility Society introduced a classification of endometriosis. This classification, based on surgical aspects of endometriosis, allows the exploration and comparisons of major publications over a period of more than 30 years with the aim of evaluating whether endometriosis in the adolescent is a hidden, progressive and severe disease.

Methods

The published literature was searched using Scopus and PubMed, focusing on the terms endometriosis and adolescence. The search of the literature was set from 1980 because the present international classification of endometriosis was originally published in 1979 by the American Fertility Society (AFS). In addition, references to major publications were included in the search. The search identified 12 manuscripts that included the description of the lesions according to the original or the 1985 revised classification (r-AFS), or to a system that could be translated into the reference classification (Goldstein *et al.*, 1980; Vercellini *et al.*, 1989; Davies *et al.*, 1993; Laufer *et al.*, 1997; Reese *et al.*, 1997; Emmert *et al.*, 1998; Bai *et al.*, 2002; Ventolini *et al.*, 2005; Stavroulis *et al.*, 2006; Roman, 2010; Vicino *et al.*, 2010; Yang *et al.*, 2012). The 12 studies included a total of 437 adolescents with laparoscopy-proven endometriosis (Table I).

Findings

A hidden disease

The prevailing symptom in all the above-mentioned 12 studies has been the presence of persistent chronic pelvic pain, despite medical treatment, under different appearances such as dysmenorrhoea, acyclic chronic pain despite and, in some cases, acute abdominal pain. Usually, these complaints have been addressed by evaluating symptoms through a careful anamnesis and a physical examination; this is followed by an attempt to treat dysmenorrhoea, usually by prescribing an oral contraceptive and/or non-steroidal anti-inflammatory drugs (Bandera *et al.*, 1995).

Table I Staging of endometriosis according to r-AFS classification in adolescents with chronic pelvic pain.

	Nr	Age range	Staging	I (%)	II (%)	III (%)	IV (%)
Goldstein *et al.* (1980)	66	10–19	K[a]	58	38	0	4
Vercellini *et al.* (1989)	18	11–19	r-AFS	67	33	0	0
Davies *et al.* (1993)	36	13–20	r-AFS	28	22	19	31
Reese *et al.* (1997)	49	11–19	r-AFS	80	12	6	2
Laufer *et al.* (1997)	32	13–21	r-AFS	77	23	0	0
Emmert *et al.* (1998)	37	11–19	M[b]	92	8	0	0
Bai *et al.* (2002)	39	14–21	r-AFS	10	44	28	18
Ventolini *et al.* (2005)	28	12–18	r-AFS	14	39	43	4
Stavroulis *et al.* (2006)	11	13–20	r-AFS	45[c]		55[d]	
Vicino *et al.* (2010)	38	15–21	r-AFS	18	13	34	34
Roman (2010)	20	14–20	r-AFS	40	45	5	10
Yang *et al.* (2012)	63	12–20	r-AFS	8	3	52	37

r-AFS, The American Fertility Society (1985).
[a]K based on the criteria of Kistner *et al.* (1977).
[b]M based on the endoscopic endometriosis classification (Mettler, 1989)
[c]Stages I and II.
[d]Stages III and IV.

In this connection it has been reported that when adolescent girls with chronic pelvic pain do not respond to the above-mentioned therapies, as in some 70% of the cases, laparoscopy will provide evidence of the presence of peritoneal endometriosis (Goldstein *et al.*, 1980; Davies *et al.*, 1993, Laufer *et al.*, 1997; Reese *et al.*, 1997). The prevalence of endometriosis in symptomatic adolescents differs among the various studies and has been estimated at between 19 and 73%, while there are no data on endometriosis in asymptomatic adolescents. Early studies suggested that endometriosis was rare during adolescence (Meigs, 1941; Haydon, 1942). This, however, was probably due to the fact that in the 1940s, diagnosis could only be made at laparotomy. Indeed, in the 1980s with the introduction of laparoscopy, it was suggested that endometriosis may not be uncommon in adolescent girls. In his report, Goldstein *et al.* (1980) diagnosed by laparoscopy the presence of endometriosis in almost 50% of adolescent girls with pelvic pain. However, endometriosis is more frequently seen in adolescents with continued pelvic pain despite treatment with analgesics and cyclic oral contraceptive pills. In 1982, Chatman and Ward (1982) prospectively analysed 43 consecutive laparoscopies in symptomatic teenagers and found a 65% prevalence of endometriosis.

A second reason for the apparent increase in the incidence over the years is the inclusion of atypical lesions, such as clear or red vesicles, in the diagnosis of endometriosis (Redwine 1987). In their series, Vercellini *et al.* (1989) identified the presence of endometriosis in almost 40% of their young patients, acknowledging that during their trial diagnostic criteria were modified to include atypical lesions. When this modification of the protocol was enacted, the prevalence of endometriosis rose to 52%. Finally, the introduction of transvaginal ultrasound (TVU) may also explain the increase in diagnosis of ovarian endometriomas in adolescents during the last two decades (Moore *et al.*, 2003).

More recently, indirect information gathered by the ACOG (2005) suggests widespread occurrence, since in ~60% of adult patients with endometriosis, symptoms started before these women reached 20 years of age. Chapron *et al.* (2011) investigated the possibility of identifying markers of 'deeply infiltrating endometriosis' especially during adolescence. They found that adolescent girls with deep endometriosis had more school absences during menstruation and more frequently, and for a longer period, used an oral contraceptives to treat severe primary dysmenorrhoea. In the early studies, serious gastrointestinal symptoms, including constipation, diarrhoea, nausea, and vomiting were sometimes reported (Goldstein *et al.*, 1980; Davies *et al.*, 1993). Acute abdominal pain and gastrointestinal dysfunction was also reported by approximately one-third of Chinese adolescents with endometriosis (Yang *et al.*, 2012).

The possibility of early onset of endometriosis-related pelvic pain prompted Batt and Mitwally (2003) to advocate using thelarche, rather than menarche, as a marker to include the possibility of endometriosis in the differential diagnosis in girls with chronic pelvic pain. The mean onset of menarche presented in five studies ranged from 11.8 to 14.2 years; on average, the onset of pain ranged from <1 to 5.9 years after menarche and in youngest girl (10.5 years old) with proven endometriosis, the onset of symptoms was 5 months after menarche (Goldstein *et al.*, 1980). The shortest interval (mean 9.4 ± 3.1 months) between menarche and the onset of symptoms was reported by Davies *et al.* (1993). In addition, in 23 girls, 'menstrual cramps' started with their earliest menstrual periods. It is remarkable that in this study, Stage III or IV endometriosis was reported in 50% of the cases. In contrast, Laufer *et al.* (1997) reported no case with class III or IV endometriosis in a study where the mean age at the time of diagnosis was similar but the mean interval between menarche and onset of symptoms was 3.8 years. This could suggest that, in addition to uterine tract anomaly, chronic pelvic pain with onset at the time of menarche represents a risk factor for severe endometriosis during adolescence. Additionally, in a recent meta-analysis, Nnoaham *et al.* (2012) concluded that menarche at an early age is associated with a modest increase in endometriosis risk.

It is a fact that the majority of adult patients with endometriosis have a history of symptoms starting during adolescence, although diagnosis is

systematically delayed (Dovey and Sanfilippo, 2010) and, even when symptoms start early in life, it may take years before a correct diagnosis is posed (Arruda et al., 2003; Nnoaham et al., 2011). Fortunately, both the medical profession and women at large are becoming more aware of the disease, making an early diagnosis more frequent (Templeman, 2009).

A progressive disease

There are several reasons why it is difficult, if not impossible, to assess the progression of endometriosis in the adolescent. First, at the time of diagnosis lesions are systematically treated by ablation or excision. When, following surgery, a second-look laparoscopy is performed, the endoscopist is often unable to distinguish between the progression of disease and post-operative adhesions. Secondly, it is well known that subtle peritoneal lesions of endometriosis may appear and disappear like mushrooms in a field (Brosens et al., 1994), but can be identified by scanning electron microscopy on biopsies from normal-looking peritoneum (Vasquez et al., 1984). Thirdly, transumbilical laparoscopy is still an invasive technique that is not suitable for second look unless there is a major clinical indication. Finally, as early as 1980, Goldstein et al. found that in adolescents endometrial lesions were similar to those observed in adults, although in 20% of their Stage I cases, the lesions were quite atypical and consisted of 'petechial-like areas on the pelvic peritoneum and uterosacral ligaments'. Also Vercellini et al. (1989) reported the presence of atypical lesions and, as already stated, in order to include them, they modified their protocol halfway through the study. Davies et al. (1993) and Reese et al. (1997) reported that 'atypical' or subtle lesions and superficial red lesions are, respectively, the most common in adolescents. When biopsies were obtained, it was noticed that the lesions were different from the typical powder-burn ones seen in adults (Goldstein et al., 1980; Davies et al., 1993; Bourdel et al., 2006).

Progression of disease in adolescents has been suggested by a few cases with second-look laparoscopy. In 2010, Unger and Laufer published the case reports of three adolescents, aged between 13 and 16 years, suffering from severe pelvic pain and diagnosed with Stage I endometriosis at the time of laparoscopy. Although the endometriotic foci were cauterized, the adolescents did not remain compliant with the menstrual suppressive therapy; they had to undergo a second-look laparoscopy which demonstrated in all three cases progression of the disease and the presence of an increase in implants onto the peritoneum; the only significant additional finding was the formation of a small endometrioma.

Reese et al. (1997) presented 39 adolescents divided in four age groups and found only endometriosis Stage I or II in the two younger age groups (11–13 and 14–15 years), but 4 patients (18%) with Stage III or IV in the two older age groups (16–17 and 18–20 years). Vicino et al. (2010) found no difference in stages of endometriosis between adolescents aged 18–19 years ($n = 12$) and 19+ ($n = 26$) and both groups had, respectively, 75 and 66% severe endometriosis; ovary was involved in 41%, and 3 cases were complicated by ovarian endometrioma. It seems that once an adolescent reaches the age of 16 years, the risk of severe endometriosis needs to be taken into account.

A severe disease

A major factor in severity of endometriosis in adolescents is its association with Müllerian anomalies. Indeed, an increased risk of early onset endometriosis is clearly linked with those anomalies producing an outflow tract obstruction. Dovey and Sanfilippo, (2010) have estimated that the incidence of endometriosis in adolescents with genital tract anomalies varies between 6.5 and 40.2%. Interestingly, non-obstructive Müllerian anomalies do not represent a risk factor for early-onset endometriosis. In the series published by Yang et al. (2012), the mean age at diagnosis was 18.4 $\pm$ 1.8 years and they confirmed that in the presence of genital tract malformations, the onset of the disease occurred earlier than in girls without anomalies (16.2 versus 19.0 years). Among 15 subjects with genital tract anomalies, they found that in 14 cases the ovaries were involved (93.3%) while the rectovaginal pouch or uterosacral ligaments were involved in only two cases (13.3%). On the other hand, among 48 cases without genital tract anomaly, 26 had rectovaginal pouch or uterosacral ligaments involved (54%; $P = 0.005$). Besides ovaries and peritoneum, endometriosis affected other sites such as the bladder and ureter. Their patients underwent surgical treatment either by laparoscopy (46/63) or laparotomy (15/63) and were debulked to Stage I or less. In the majority of the 15 cases with genital tract malformations, surgical correction was carried out, but in 3 patients, the malformations were so severe that hysterectomy had to be performed.

Table I summarizes staging of endometriosis at laparoscopy in the 12 studies. They are based on the r-AFS classification (The American Fertility Society, 1985) except for the studies by Goldstein et al. (1980) and Emmert et al. (1998) which were based on other systems (Kistner et al., 1977; Mettler et al., 2001). The main finding is the higher incidence of severe endometriosis (Stages III and IV) in the more recent reports. Whereas older publications (with one exception) dealt mostly with early stages, more recent studies report almost invariably a large number of cases with Stage III and IV endometriosis. Severe stages in adolescent endometriosis relate in particular to extensive tubo-ovarian adhesions and endometrioma formation. Four out of six early studies (Goldstein et al., 1980; Vercellini et al., 1989; Laufer et al., 1997; Emmert et al., 1998) reported a total of 153 girls with endometriosis and only 3 had Stage III or IV disease. Davies et al. (1993) reported on 36 cases with early onset endometriosis with symptoms starting at the time of menarche; nonetheless, diagnosis was posed at the mean age of 16.6 years; at the time of laparoscopy, 50% were found to have Stage I or II and 50% had Stage III or IV. The more recent studies show clearly that endometriosis in the adolescent is no longer a disease of subtle superficial lesions, but is also characterized by severe stages, including extensive adhesions and ovarian endometriomas. Although the publications suggest more severe endometriosis in the latter in comparison with the former studies, the progress can be at least partially explained by improvement of diagnostic tools such as ultrasound. The effect of severe endometriosis on fecundability was investigated by Ventolini et al. (2005) in a long-term (8.6 years) follow-up of 28 adolescents with Stages I–IV, comparing mild and severe forms. In these young women, a diagnosis of endometriosis (through laparoscopy and biopsies) was made during the evaluation of the cause of chronic pelvic pain that did not respond to medical treatment. No other interventions beside diagnosis were performed. The original staging of endometriosis was done at the time of the surgery, using the rAFS standard classification system. All subjects were treated with the same regimen, an uninterrupted combined oral contraceptive for 6 months; they were then followed-up for a period of 8.6 years. During this follow-up, they found a linear decrease in fecundability with each r-AFS stage: Stage I (75%); Stage II (55%); Stage III (25%) and Stage IV (0%) ($P < 0.05$). However, it is noteworthy that a clear

causal relationship between endometriosis and infertility has not yet been established, except in the case of the presence of extensive adhesions (Pritts and Taylor 2003).

Commentary

The appreciation of the incidence of endometriosis in adolescents is severely biased by the necessity of laparoscopy for diagnosis. In theory, the introduction of ultrasound in the 1990s may have improved the selection of symptomatic adolescents with ovarian endometrioma; however, no data exist on the true onset of endometriosis in adolescent girls and on the length of its asymptomatic stage.

Endometriosis in the adolescent is in the early stages characterized by the presence of subtle, red and vesicular lesions and adhesion formation on the ovarian surface and the pelvic peritoneum. According to Evers *et al.* (1998), in its early phases endometriosis is a dynamic disease, with subtle, atypical lesions (clear, red, black) emerging and vanishing again because, in a majority of cases, the peritoneal defence system can often contain the spread of ectopic endometrial foci.

At the same time, the eutopic endometrium, at least in the adult suffering from endometriosis, is in many ways different from that of healthy controls both in the proliferative and secretory phases (Kao *et al.*, 2003; Brosens *et al.*, 2012). Molecular aberrations include a local estrogen production sustaining the implants. In addition, there is a condition of 'progesterone resistance' and vascular events are often disrupted in endometriosis, with an overall increase in angiogenesis. These changes led to the suggestion that progression of endometriosis may depend on the ability of the endometrium to survive owing to a series of molecular abnormalities that include modifications of the immune cell population, aberrant expression of aromatase, dysregulation of interleukin-6 production, impaired temporal expression of beta3-integrin, and HOX genes and reduced spontaneous apoptosis (Brosens *et al.*, 2012). Clearly, no data are available on uterine changes in adolescents with endometriosis.

It has been claimed that adolescent endometriosis is no different from adult endometriosis (Roman, 2010; Vitonis *et al.*, 2010). However, there are likely to be differences in the morphological types of lesions. Several authors noted that adolescent endometriosis differs by the high percentage of subtle, clear, red or vesicular implants. Another major difference is the rarity of the deep ($>$ 5mm) or adenomyotic type of endometriosis in adolescents. Davies *et al.* (1993) reported that infiltrating endometriosis occurring in pelvic structures of adolescents was characterized by glands and stroma with associated fibrosis of 3–5 mm in thickness. These lesions may suggest early stages of deep endometriosis, but differ histologically from the deep lesions as defined by Cornillie *et al.* (1990) and Koninckx *et al.* (1991). Interestingly, in adolescent girls, peritoneal pockets with endometriosis were observed in 6 (17%) out of 36 cases by Reese et al. (1997). Progression of disease in the adolescent appears to be primarily characterized by extensive adhesions and endometrioma formation.

It is clear that more research is needed on the pathogenesis of adolescent endometriosis. The pathogenesis is complex as lesions can occur both before menarche and early after it (Marsh and Laufer 2005). Menstruations play a major role since, according to Goldstein *et al.* (1980) symptoms such as pelvic pain usually occur $<$3 years following menarche and the disease is more severe in the presence of genital outflow obstruction. Brosens and Benagiano (2013) have recently formulated the hypothesis that endometriosis manifesting itself in the premenarcheal or adolescent period may develop from endometrial stem cells present in the endometrial shedding which typically occurs in 5% of the neonates after birth (Huber, 1976). The lesions may develop through VEGF stimulation of angiogenesis associated with the initial ovarian activity preceding the menarche (Brosens and Benagiano, 2013). The extensive angiogenesis may result in petechial lesions and adhesion formation (Brosens *et al.*, 2004). Unfortunately, subtle lesions and filmy adhesions are underestimated by laparoscopy as the pneumoperitoneum causes collapse not only of the microvascularization, but also of the filmy, free-floating adhesions on the peritoneal and ovarian surfaces. However the use of hydroflotation, as suggested by Laufer *et al.* (1997), prevents the collapse of the vascular new network and of filmy adhesions and allows appreciation of the presence and extent of subtle lesions.

The recent reports on endometriosis in adolescents reveal an unexpected degree of severity as staged by the r-AFS classification system. According to recent studies, endometriosis affects 35–54% of the symptomatic girls and the majority have a severe Stage III or IV. Most importantly, the severe cases include extensive tubo-ovarian adhesions and ovarian endometriomas. Given this reality of severity, it is of critical importance to elucidate how the delay in diagnosis can be reduced thereby preventing severe ovarian disease and a decrease of fecundability. Less invasive diagnostic techniques have been developed in recent years and should be introduced in adolescent gynaecology. Moore *et al.* (2003) concluded that TVU can accurately confirm or exclude the presence of an ovarian endometrioma. Secondly, transvaginal hydrolaparoscopy has been developed more than 10 years ago as an outpatient technique for pelvic investigation in infertility. The use of saline as the distension medium causes less discomfort than CO_2 insufflation. The technique has been shown to have six important advantages. First, the needle technique is a safe endoscopic procedure performed in an ambulant operative setting (Gordts *et al.*, 1998, Darai *et al.*, 2000, Gordts *et al.*, 2001, 2004). Secondly, the transvaginal approach gives direct access to the tubo-ovarian structures. The restricted visualization of the pelvic peritoneum may be a disadvantage, but there is no evidence that ablation of all peritoneal endometriosis is effective, or even realistic (Wright *et al.*, 2005; Healey *et al.*, 2010). Thirdly, the distension by saline and hydroflotation improve visualization of adhesions and microvascularization (Brosens *et al.*, 2001). Fourthly, the acceptability of transvaginal needle access is likely to be higher than the incisional transumbilical access for the adolescent. Roman (2010) noted that in New Zealand 60% of adolescents are sexually active, which suggest that transvaginal access for adolescent endoscopy is acceptable in a majority of circumstances. Fifthly, atraumatic reconstructive surgery of implant lesions, adhesions and ovarian endometriomas up to the size of 4 cm can be performed by transvaginal access (Gordts, 2013). Sixthly, and probably most important, a second-look transvaginal endoscopy after 1 or 2 years can be systematically recommended. Unfortunately, the transvaginal technique is not widely used in routine gynaecology, although it would allow the diagnosis at an earlier stage with additional ovarian surgery when indicated and a systematic second-look endoscopy to evaluate the effect of surgical and/or medical treatment.

The pathophysiology of severe endometriosis in the adolescent remains a mystery. Recently, Burghaus *et al.* (2011) carried out a case–control study in which 595 adult women with laparoscopically confirmed endometriosis were matched with 475 controls; this yielded 298 cases and 300 controls. They were able to identify a series of predictors of endometriosis, such as duration of the menstrual cycle and bleeding, number of pregnancies and spontaneous abortions, and smoking

status. They also showed that a number of factors, such as age at menarche, number of live births, ever use of oral contraceptives and body mass index, were non-predictive. The situation seems different when dealing with adolescents. Although, Laufer et al. (1997) reported a similar age of menarche for adolescents with and without endometriosis, menstruation in general and BMI have been identified as the two most relevant variables involved in the development of endometriosis in adolescence. In contrast for adult women, with regard to BMI, an inverse association has been reported with the risk of suffering from endometriosis: Hediger et al. (2005) studied a laparoscopy cohort and found that patients with endometriosis had both a history of lower BMI and a lower BMI at the time of diagnosis. Vitonis et al (2010) used data from the Nurses' Health Study II to clarify the association between BMI during childhood and early adulthood endometriosis. They observed that the incidence of endometriosis was significantly reduced with increasing body size. This difference remained significant even after adjusting for age, birthweight, age at menarche, parity, use of oral contraceptive and adult BMI. Finally, Lafay Pillet et al. (2012), in a prospective case–control study involving 476 subjects matched for age and smoking status, found that patients with deep infiltrating endometriosis had a markedly lower body mass index than controls.

On the vital issue of disease progression or changes in lesion appearance as age progresses and adolescents become adults, data in the literature are very limited. In 2009, Doyle et al. conducted a retrospective study of 90 surgically treated adolescents who, in spite of being on continuous medical treatment, experienced pain recurrence and even exacerbation of pain and therefore opted for a second-look laparoscopy. This found no r-AFS stage change in 70% of patients after a median post-surgery time of 29 months.

Unfortunately, the retrospective nature of most studies, with a frequent lack of control groups prevent us from drawing conclusions on the effectiveness of medical or surgical or treatments in controlling disease progression. Tandoi et al. (2011) have attempted to evaluate the likelihood of long-term recurrence of endometriosis in young subjects. They found a linear progression of recurrence rates with time from the initial surgery, although there was no association with the rate of recurrence of endometriosis-related symptoms, site/stage of the disease, type of surgery and post-surgical medical treatment. Therefore, the natural history of an adolescent who is diagnosed with stage I endometriosis remains a challenging issue in modern gynaecology.

Conclusion

Notwithstanding the difficulty in drawing any definite conclusions from incomplete evidence and occasionally even contradictory results, recent findings indicate that an early onset of chronic pelvic pain at the time of menarche represents a risk factor for severe endometriosis during adolescence. In addition, when endometriosis appears during adolescence, there is likelihood that the disease will progress and, if left untreated, produce adverse effects that go beyond pain, and include infertility. Finally, a majority of adolescent girls with chronic pelvic pain not responding to conventional medical therapy have endometriosis. For all these reasons, an early identification of the disease may go a long way in slowing or preventing progression.

Indeed a number of medical and surgical options exist today for the treatment of endometriosis. An early mini-invasive diagnostic procedure in adolescents with untreatable chronic pelvic pain will lead the gynaecologist to an early identification of endometriosis, followed by a personalized treatment. Given what we know, this seems the best way to guide and protect adolescent girls in these circumstances.

Authors' roles

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Conflict of interest

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