

# The clinical diagnosis of pelvic endometriosis in adolescents

## Abstract

We present a review of available diagnostic tools for adolescent endometriosis, a condition that may have a different pathogenesis than the adult form and therefore necessitates specific methodologies. The new theory provides that endometrial stem/progenitor cells in neonatal uterine bleeding may be causally linked to early-onset endometriosis, thereby explaining both the occurrence in pre-menarcheal girls and its severity in some adolescents. Severe disease seems characterised by the presence of ovarian endometrioma. Disagreement exists in published studies and among specialists on the seriousness and tendency to progress of adolescent endometriosis: some investigators have published series where the vast majority of cases were stage I and II, whereas, others have presented cohorts in which severe disease was relatively frequent. The first and most important sign indicating the possible presence of endometriosis is treatment-resistant dysmenorrhea, to the point that it seems possible to predict an increased risk of endometriosis in girls with an early-onset of this symptom. At the same time, dysmenorrhea alone cannot be sufficient for a proper diagnosis. Therefore, clinical conditions that may increase the occurrence of neonatal bleeding may represent additional signs of an increased risk of early-onset endometriosis. Among them, preeclampsia, postmaturity, feto-maternal incompatibility and low birth weight at or around term.

**Keywords:** adolescent endometriosis, dysmenorrhea, diagnosis, neonatal uterine bleeding, imaging techniques, progression

Volume 4 Issue 3 - 2017

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**Received:** October 28, 2016 | **Published:** March 02, 2017

## Introduction

Endometriosis is one of the most frequent benign diseases of adult women. Its prevalence is difficult to evaluate and has been reported as 5% overall in the Nurses' Health Study II prospective cohort, with the highest incidence among women aged 25-29 years.<sup>1</sup> Other studies placed the prevalence of mainly asymptomatic endometriosis at between 1 and 10 percent.<sup>2-5</sup> The diagnosis is usually made in adult women suffering from chronic pelvic pain or infertility. In a recently published essay, Vercellini et al.<sup>6</sup> have critically reviewed present diagnostic interventions for the detection of endometriosis, stating that today these interventions are carried out "with defined harms and uncertain benefits, or whose effectiveness is comparable with less expensive alternatives". Specifically, they expressed the opinion that a non-surgical diagnosis of endometriosis can be based on symptoms, physical findings and transvaginal ultrasonography (TVS) in most patients with symptomatic disease. Whereas, much can be said in favor of a new, less invasive approach, two considerations are in order: first, until now, non-invasive techniques, are properly validated (something, by the way, that Vercellini et al.,<sup>6</sup> advocate) research protocols must continue to rely on laparoscopic findings, followed by histological confirmation. Secondly, we believe that adolescent endometriosis represents a special case that must be dealt with the utmost care. This is because, as matters exist today, diagnosis may be delayed even for years, causing concern in view of the fact that in some instances the disease may progress and even impair future fertility.<sup>7</sup> In addition, there are reasons to suggest that early-onset endometriosis may have a different origin than the adult form, being due to the occurrence of neonatal uterine bleeding (NUB).<sup>8,9</sup>

## Search strategy and analysis

The present Review is based on a search of the literature via Scopus and PubMed undertaken using the key words "adolescent endometriosis" "non-invasive diagnosis of endometriosis" "dysmenorrhea in endometriosis", "deep pelvic pain" "symptoms of endometriosis". In addition, references were examined in published papers on related topics. Table 1 shows the results of the search.

## Symptoms and signs

Efforts have been made to develop tools for an early and accurate detection of pelvic endometriosis in adult women.<sup>10</sup> Whether or not such tools are developed, the question remains to which extent adolescent endometriosis is caused by NUB or, like in adults, by menstrual bleeding. In other words, whether or not the two conditions can be equated. Unfortunately, this question will only be answered when routine registration of uterine bleeding in the neonate will be implemented. Here, after reviewing the severity of endometriosis in the adolescent, we intend to present a scoping review of the symptoms and signs of adolescent endometriosis with the goal of improving its clinical diagnosis. Harel et al.<sup>11</sup> estimated that pelvic abnormalities, such as endometriosis, or uterine anomalies might be found in approximately 10% of adolescents with severe dysmenorrheal symptoms. A systematic review by Janssen et al.,<sup>12</sup> based on 15 selected studies found that the overall prevalence of visually confirmed endometriosis was 62% (543/880; range 25-100%) in all adolescent girls undergoing laparoscopic investigation, 75% (237/314) in girls with Chronic Pelvic Pain (CPP) resistant to treatment, 70% (102/146) in girls with dysmenorrhea and 49%

(204/420) in girls with CPP not necessarily resistant to treatment. Starting with these prior observations a Scopus search was carried out using as key words “endometriosis” and “adolescents”; this revealed for the period starting in 1995 a total of 1.274 publications. The key words “signs” or “symptoms” reduced the number to 293. In all these publications, dysmenorrhea was the main symptom,

but as dysmenorrhea is the most common gynecologic complaint among adolescent girls, in order to be considered as suggestive of the presence of endometriosis dysmenorrhea was qualified as being “resistant to conventional medication”, or “of early onset”. This new group of publications was screened for title and abstract and revealed 10 original studies (Tables 1) (Table 2).

**Table 1** Number of publications scrutinized for the period 1995 till 2016

|  |      |
|--|------|
| “Endometriosis” & “adolescent”         | 1274 |
| “Sign” or “symptom”                    | 293  |
| “Dysmenorrhea” or “Deep pelvic pain”   | 98   |
| “Ultrasounds for endometriosis”        | 112  |
| “Magnetic resonance for endometriosis” | 88   |

**Table 2** Selection of original studies mentioning symptoms

| Author                          | Year | Findings   |
|---------------------------------|------|--|
| Laufer MR et al. <sup>17</sup>  | 1997 | A retrospective study describing cases who: (1) responded to conventional medical therapy; (2) did not respond to non-steroidal anti-inflammatory drug and an oral contraceptive pill, and (3) underwent a laparoscopy to determine the etiology of the pelvic pain. More than two thirds of the study population (69.6%) was found to have endometriosis. |
| Emmert, et al. <sup>18</sup>    | 1998 | A case series of adolescents with chronic or acute pelvic pain and right-sided lower abdominal pain. Laparoscopically diagnosed.   |
| Stavroulis et al. <sup>19</sup> | 2006 | A retrospective review of case records describing frequency and severity of endometriosis in adolescent and teenager girls with chronic pelvic pain who fail to respond to medical treatment a group and early results are encouraging.  |
| Nagle et al. <sup>16</sup>      | 2009 | A case control study of women with endometriosis showing that they are more likely to be thinner and underweight. Data suggest that being overweight during late childhood is associated with the development of endometriosis.  |
| Vicino et al. <sup>20</sup>     | 2010 | A prospective clinical study of 38 young women aged $\leq 21$ years with surgically confirmed diagnosis of endometriosis Pelvic pain was present in all cases.   |
| Treloar et al. <sup>15</sup>    | 2010 | Case control trial. Found a decreased risk of endometriosis with late age at menarche and an increased risk in women who report an early onset of dysmenorrhea.  |
| Chapron et al. <sup>21</sup>    | 2011 | Cross-sectional study. Found that more positive family history of endometriosis (odds ratio [OR] = 3.2; 95% confidence interval [CI]: 1.2-8.8) and more absenteeism from school during menstruation (OR=1.7; 95% CI: 1-3) in adolescents with endometriosis. Advocated use of Oral Contraceptives for treating severe primary dysmenorrhea                 |
| Smorgick et al. <sup>23</sup>   | 2013 | Retrospective review of medical records of 138 adolescents/young women who were less than age 24 years. Comorbid pain syndromes were found in 77 (56%), mood conditions in 66 (48%), and asthma in 31 (26%) of the subjects.   |
| Janssen et al. <sup>12</sup>    | 2013 | The overall prevalence of visually confirmed endometriosis in 15 studies was 62% (range 25-100%) in all adolescent girls under going laparoscopic investigation; 75% in girls with Chronic Pelvic Pain (CCP) resistant to treatment; 70% in girls with dysmenorrhea and 49% in girls with CPP not necessarily resistant to treatment.                      |
| Zannoni et al. <sup>13</sup>    | 2014 | Cross-sectional study. A significant association was found between severe dysmenorrhea, absenteeism from school/work, and basic level of education.  |

## Dysmenorrhea and chronic pelvic pain

Dysmenorrhea is a serious problem in adolescence. Zannoni et al.<sup>13</sup> recently reported on 250 young women aged 14-20 years, 68% of whom complained of dysmenorrhea. They found a significant association between severe pains and absenteeism from school/work. The adjusted odds ratio for severe dysmenorrhea was about 28 times greater than in those who did not declare absenteeism (95%CI 7.898-98.920,  $P<.000$ ). Also Chapron et al.,<sup>14</sup> found in 229 young patients with histologically-confirmed endometriosis and severe and lasting dysmenorrhea, more absenteeism from school during menstruation (OR=1.7; 95% CI:1-3). It seems possible to predict an increased risk of endometriosis in girls with an early-onset dysmenorrhea: Treloar et al.,<sup>15</sup> carried out a case-control study including 268 women with surgically confirmed moderate to severe endometriosis and 244 women without endometriosis. They observed that a history of dysmenorrhea was associated with subsequent endometriosis (odds ratio, 2.6; 95% confidence interval, 1.1-6.2). They also found that menarche after age 14 was strongly and inversely associated with endometriosis (odds ratio, 0.3; 95% confidence interval, 0.1-0.6). The same group also observed that being overweight at 10 years increased the risk of endometriosis (OR 2.8; 95% CI 1.1-7.5), although these results require confirmation in large population studies.<sup>16</sup>

In spite of these findings, our systematic review of the relationship between adolescent dysmenorrhea and the presence of endometriosis yielded conflicting results, as shown in Table 2. In 1997, Laufer et al.,<sup>17</sup> systematically investigated patients younger than 22 years referred to them because of chronic pelvic pain not responding to either non-steroidal anti-inflammatory drugs (NSAID) or oral contraceptive pills (OC) and submitted them to laparoscopy to determine its etiology. They observed that 69.6% of these young women had endometriosis, either stage I or II (r-ASRM classification). In the vast majority (90.6%) of them pain was acyclic or both cyclic and acyclic. The following year, Emmert et al.,<sup>18</sup> examined through laparoscopy/pelviscopy 105 adolescent girls with pelvic pain (mean age of 17.3; range 11-19 years). They found endometriosis in 35.2% of them, in the vast majority (97.8%), stage I. More recently, different results were obtained: Stavroulis et al.,<sup>19</sup> evaluated 31 teenager girls referred for CPP who failed to respond to NSAID or OC. No pelvic abnormalities were detected in 35.5% of them, whereas an equal proportion (11 subjects) had endometriosis, 6 of them severe. Vicino et al.,<sup>20</sup> studying 38 young women  $\leq 21$  years with a surgically confirmed diagnosis of endometriosis found that pelvic pain was present in all cases, although in 3 subjects surgery was carried out for reasons other than CPP. In three of their subjects, an ovarian endometrioma was present and they state that "the frequency of minimal-mild endometriosis was lower than in adult cases observed in the experience of GISE (the Italian Group for the Study of Endometriosis)".

Chapron et al.,<sup>14,21</sup> confirmed that a history of early-onset, severe and lasting dysmenorrhea refractory to NSAID and requiring the use of OC is a strong predictor of endometriosis. They also claimed that additional associations exist between certain symptoms in adolescence and the later development of endometriosis. Studying 229 young patients with histologically confirmed endometriosis, they observed that those with deep, infiltrating endometriosis had significantly more positive family history of endometriosis (OR=3.2; 95% CI: 1.2-8.8) and, as mentioned above, more absenteeism from school during menstruation. These young women used OC for treating their severe primary dysmenorrhea more frequently (OR=4.5; 95%

CI: 1.9-10.4) and for longer periods ( $8.4\pm 4.7$  years vs.  $5.1\pm 3.8$  years). Finally, more of them started use of OC before age 18 (OR=4.2; 95% CI: 1.8-10.0). One issue that needs to be taken into consideration is the fact that focusing on dysmenorrhea as the main indication for laparoscopic investigation may have influenced the early findings of predominantly subtle superficial lesions in adolescents. Indeed, ovarian endometriomas were not identified unless they were present as large ovarian cysts and one such large endometrioma was diagnosed in a pre-menarcheal girl.<sup>22</sup> It is the use of imaging techniques that made it possible to diagnose an increasing number of ovarian endometriomas with ovarian adhesions, a reality that deserves full attention since, although progression of the disease is unpredictable, it has been shown that it can occur in a sizeable proportion of cases.<sup>7</sup>

In the already mentioned, recent, retrospective cohort study reporting on 86 adolescents or young women ( $\leq 22$  y), Smorgick et al.,<sup>23</sup> found early stage I or II disease in 66 (76%) and advanced stage III or IV in 20 (23%). The pathology with advanced stage endometriosis included ovarian endometriomas in 14 cases, rectovaginal nodules in 1 case and diaphragmatic and pulmonary endometriosis in 1 case. The group of women with advanced stage was found to be slightly older at the time of diagnosis than those with milder disease, suggesting that adolescent endometriosis may be a progressive disease when affecting the ovaries. The situation was even worse in the cases ( $\leq 20$  y) reported by Yang et al.,<sup>24</sup> who documented stage I or II disease in only 11% of their patients, with 89% being at stage III or IV. It is interesting to note that by comparing the clinical features of the endometrioma in adolescents to those of women of older age groups, Lee et al.,<sup>25</sup> found that adolescents experienced menarche at a significantly earlier age and that the main symptom is pain. They therefore confirmed the already-mentioned general observation of Treloar et al.,<sup>15</sup> that late menarche is inversely associated with endometriosis. It is absolutely true that it is impossible to predict in which case the disease will progress, but-given the present delay in diagnosis - when symptoms persist for years - there is a clear possibility that the disease is progressing.

Especially worrying is ovarian endometriosis in adolescents: data available up to 2013 indicate that 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. This is indirect, but strong evidence of a tendency of the disease to progress and produce early damage.<sup>7</sup> Yang et al.,<sup>23</sup> seem to be the only to have published data on recurrence on 35 adolescents in their series of 63 cases. Their mean follow-up was 46.3 months (range 12-98) and they defined recurrence 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 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 60% of 15 adolescents who were not treated post-operatively; in 46% of 13 who received an oral contraceptive medication; in 1 of the 2 subjects given a progestin and in none of the 5 treated with a GnRH analogue. The difference between untreated and GnRHA-treated subjects was statistically significant ( $P=0.038$ ).

## Other markers

Under these circumstances, as suggested by Chapron et al.,<sup>14</sup> additional parameters besides dysmenorrhea need to be explored for the early detection and treatment of ovarian endometriomas. Today the minimum diameter suggested to warrant intervention according

to the European Society of Human Reproduction and Embryology (ESHRE) guidelines is 3 cm; this however has been arbitrarily chosen on the assumption that below that size an image may represent a dysfunctional hemorrhagic cyst.<sup>26</sup> The problem is that current guidelines are based on observations in the adult and do not represent the situation in adolescents and young women. Consequently, the rationale for investigating other factors than dysmenorrhea that may be linked with an increased risk of endometriosis in adolescents and young women resides in the poor value of existing signs.

## Diagnostic Tools

Today invasive and non-invasive diagnostic procedures exist and, clearly, in an adolescent, whenever feasible non-invasive tools should be preferred.

## Imaging techniques

When dealing with adolescents, preference should be given to non-invasive methods offering an accurate diagnosis of the presence, type, location and extent of endometriotic lesions. Two techniques are today the most frequently utilized: transvaginal sonography and magnetic resonance imaging. Both can identify and characterize severe endometriotic lesions, but unfortunately, there is virtually no information on data in adolescents. The issue is complex and recently Kelleher and Goldstein<sup>27</sup> pointed out that in order to carry out a proper differential diagnosis for adnexal masses in childhood, the pediatrician needs to broadly know the wide range adnexal pathology. This includes ovarian cysts and tumors (benign or malignant), fallopian tube cysts and abscesses, paratubal cysts, and endometriomas. A correct diagnosis requires consideration of the patient's age, presenting complaints, physical examination findings, and imaging results; only following a careful evaluation of these variables it becomes feasible to generate a list of possible diagnoses and an appropriate treatment plan.

**Transvaginal sonography:** For over two decades TVS has been utilized extensively for a non-invasive diagnosis of ovarian endometriomas. In 1989, Athey et al.,<sup>28</sup> documented the sonographic features of pathologically-proven ovarian endometriomas in 32 patients and found acoustic enhancement in 88% of the cases. Describing internal echo texture, they observed that 80% of the endometriomas were predominantly or totally anechoic; only 4 contained septations; 12 contained scattered internal echoes, with or without septations; and 9 contained dependent echoes, with or without septations. They concluded that the overall appearance simulated that of hemorrhagic ovarian cysts, but occasionally ultrasonographic features resembled those of a tubo-ovarian abscess, cystadenoma, cystadenocarcinoma, or ectopic pregnancy.

In another early series published in 1992, consisting of 37 pathologically-proven endometriomas, Kupfer et al.,<sup>29</sup> described what they considered a very specific finding: the presence of a homogeneous hypo-echoic "carpet" of low-level echoes, either diffused, or in one or several loculations of a multiloculated cystic mass. This picture was observed in 82% of their cases and was considered characteristic although not pathognomonic of an endometrioma. Starting in 1993, several reports began to appear: Fried et al.,<sup>30</sup> analyzed 51 cases of histologically-proven endometrioma and attempted a classification, dividing them as:

i. Purely cystic (30% of their cases),

- ii. Cystic with various degrees of complexity with septation or debris (62%),
- iii. Essentially solid (8%).

This was followed by the first of a series of publications by a Group in Sardinia who set-up a trial aimed at assessing the efficiency of TVS in distinguishing endometriomas from other ovarian cystic structures. They concluded that TVS had an efficiency of 88% in differentiating endometriomas from other ovarian masses with a specificity of 90%.<sup>31</sup> A year later, Kurjak and Kupesic published the results of a 5-year prospective study involving 656 patients with benign and malignant adnexal masses, 103 of which were subsequently proven to be ovarian endometriosis. It utilized a new "Scoring system for prediction of ovarian endometriosis based on transvaginal color and pulsed Doppler sonography". The system consists of a combination of clinical signs and symptoms, measurement of circulating CA-125 levels, sonographic findings, and use of transvaginal color and pulsed Doppler to identify ovarian endometriomas. Their results indicate that the scoring system distinguished ovarian endometriosis from other benign and malignant ovarian lesions, with a sensitivity of 99.02% and a specificity of 99.64%. This compared with a morphological sensitivity of 83.91% and specificity of 97.12%.<sup>32</sup> Over the next decade, a relatively large number of studies confirmed these early results and in 2006, Okaro et al. applied TVS to reduce the need for laparoscopy in women with chronic pelvic pain (CPP).<sup>33</sup> In a total of 120 women they documented "hard markers" (i.e. anatomical abnormalities e.g. endometrioma or hydrosalpinx), as well as "soft markers" (i.e. reduced ovarian mobility and site-specific pelvic tenderness). The likelihood ratio for the hard markers was infinity (specificity was 100%), for the soft markers 1.9 (95% CI 1.2-3.1) and for a 'normal' ultrasound 0.18 (0.09-0.34). The pre-test probability of pelvic disease in the population of women with CPP was 58% and this probability of disease was raised to 100% with the presence of hard markers and to 73% with the presence of soft markers. The pre-test probability of 58% fell to 20% when ultrasound finding was found to be normal.

More recently an attempt was made to establish the ultrasound characteristics of endometriomas in pre- and postmenopausal patients: the International Ovarian Tumor Analysis (IOTA) screened 3511 patients using a standardized research protocol.<sup>34</sup> All patients were scanned transvaginally by an experienced sonologist following a strict research protocol. Only patients who had the adnexal mass surgically removed within 120 days after the ultrasound examination were included and the histological diagnosis was based on the removed specimen. Of all subjects included in the study, 713 (20%) had endometriomas varying in largest lesion diameter between 38 and 71mm. Fifty-one per cent of the endometriomas were unilocular cysts with ground glass echogenicity of the cyst fluid. These characteristics were found less often among a small set of endometriomas (4%) in postmenopausal patients. According to the study the optimal rule to detect endometriomas was "an adnexal mass in a premenopausal patient with ground glass echogenicity of the cyst fluid, one to four locules and no papillations with detectable blood flow". Based on clinical considerations, the following rule "premenopausal status, ground glass echogenicity of the cyst fluid, one to four locules and no solid parts" was accepted as the preferred criterion for the diagnosis.

Exacoustos et al.,<sup>35</sup> in their recent review state that the "subjective impression by an experienced sonologist for identifying endometriomas by ultrasound showed a high accuracy". They went on



affirming that even adhesions can be evaluated by “real-time dynamic TVS using the sliding sign technique, to determine whether the uterus and ovaries glide freely over the posterior and anterior organs and tissues”. This makes TVS very appealing in young women with uncontrolled pain, limiting the recourse to laparoscopy, which - as evidence proves - is a deterrent in adolescence, delaying diagnosis by many years. At the same time, one has to be aware that ovarian endometrioma, at least in the adult, rarely occurs alone and in most cases is part of more extensive pelvic endometriosis involving the posterior cul-de-sac and bowel.

**Magnetic resonance:** In an early investigation aimed at assessing the role MRI in evaluating the adnexa, Mitchell et al.,<sup>36</sup> retrospectively reviewed the examination of a total of 61 adnexal masses; whenever available, MR images were compared with ultrasound and/or computerized tomography. Using T1-weighted imaging they were able to detect signal characteristics of blood in endometriomas or in hemorrhagic cysts. They concluded that MRI provided both additional information and increased diagnostic confidence compared to ultrasound or computerized tomographic scans. The same year, 1987, Nyberg et al.,<sup>37</sup> attempted to determine in 40 pathology-proven masses, whether MR can distinguish hemorrhagic from non-hemorrhagic lesions. Their ‘hemorrhagic group’ included functional ovarian cysts (n.=7), cystadenomas (n.=7), endometriomas (n.=3), hemato-salpinx (n.=1), ectopic pregnancy (n.=1), and parametrial extension from cervical carcinoma (n.=1). They found that high signal intensity on a T1-weighted spin echo sequence represented a reliable indicator of hemorrhage, as it was present in all 14 hemorrhagic lesions. The high intensity signal was present in only four of the 26 non hemorrhagic masses (three were fat-containing dermoid cysts and one a simple cyst with adherent mesenteric fat).

Subsequently, a large series of 94 pathology-diagnosed cystic ovarian masses was published by Nishi et al.,<sup>38</sup> with the specific intent to identify ovarian endometriomas among them. They selected 6 diagnostic parameters for their evaluation:

- i. Laterality
- ii. Delineation of the cyst
- iii. Presence or absence of septal images
- iv. Homogeneity
- v. Signal intensity
- vi. T1 value of the cyst’s content

They observed homogenous internal patterns in 95.5% of endometrial cysts, with signal intensity at least equal if not higher than that of myometrium. This allowed 100% differential diagnosis with follicular, para-ovarian and corpus luteum cysts; 95.0% accuracy with serous cystadenomas and 90.9% with mucinous cystadenomas, where cyst’s content showed either lower or similar signal intensity than the myometrium. More problematic was the distinction with dermoid cysts, which in 93.1% of the cases showed heterogeneous and widely ranging signal intensity. They concluded that all endometrial cysts could be clearly defined from the other pelvic structures and exhibited a characteristic homogenous high signal intensity of the fluid with a diagnostic accuracy of 96.8%. In 1991 a review of MR imaging of the pelvis was carried out by Scoutt et al.,<sup>39</sup> who - starting with anatomy of the normal organs-carefully analyzed the situation in cases of endometriosis. They concluded that “the US appearance of

endometriosis is neither sensitive nor specific” and-quoting Friedman et al.,<sup>40</sup>- fixed at 11% US sensitivity for endometriosis in general. In contrast, they positively stated that “when multiple cystic lesions with signal behavior indicative of hemorrhage are visualized on MRI, endometriosis is the sole diagnosis”.

The already mentioned early study by Ascher et al.,<sup>41</sup> evaluated a total of 59 endometriomas (26 large and 33 small); conventional MRI identified 23 large and six small endometriomas and the FS methodology, in conjunction with gadolinium-enhanced T1FS, detected 24 large and 14 small lesions. A careful summary of MRI findings in case of ovarian endometriomas was presented in 1997 by Bis et al.,<sup>42</sup> they mentioned that an endometrioma ( $\geq 1$  cm in diameter) appears on T1-weighted images as a homogeneously hyper-intense mass and on T2-weighted images as a low-signal-intensity mass with areas of high signal intensity. They believed that even small endometriomas of less than 1 cm in diameter can be identified when a cystic lesion is hyper-intense on T1-weighted images irrespective of its appearance on T2-weighted images. Bowel and bladder involvement should be suspected if areas of high signal intensity are present on these structures. They concluded that laparoscopy and MRI can play a complementary role in diagnosing endometriomas. Additional criteria for the identification of endometriotic cysts were laid-down by Kinkel et al.<sup>43</sup>

Since 1996, several investigators focused on the possibility of identifying the presence of blood in cystic images observed at MRI. Takahashi et al.,<sup>44</sup> tried to evaluate through MRI the cystic content characteristics of endometrioma in 36 lesions from 24 patients subsequently submitted to laparoscopic or laparotomic confirmation. They calculated the density and iron concentration in the cyst and the signal intensity (SI) of MRI and found that they were directly proportional. In particular, iron concentration and the T2SI/MSI ratios were inversely proportional. A decade later, Takeuchi et al.,<sup>45</sup> applied to endometriomas a technique new at the time, “Susceptibility-weighted MRI”, combining magnitude and phase information from fully velocity-compensated gradient-echo sequences. Such a technique is able to depict as signal voids the susceptibility effects caused by local inhomogeneity of the magnetic field. They studied 60 cases of pathology-proven ovarian cystic lesions, composed of 42 endometriomas and 18 non-endometrial cysts, evaluating hemosiderin deposition within the walls of endometriomas.

They observed punctate or curved linear signal voids along the cyst wall in 92.9% of the endometriomas; these characteristics were absent in non-endometrial cysts; 41 endometriomas (97.6%) were correctly diagnosed with susceptibility-weighted MRI. Recently, Corwin et al.<sup>46</sup> reviewed data on 74 pathology-confirmed cystic hemorrhagic adnexal lesions with hyper-intense signal on T1-weighted images in 56 women, excluding lesions with solid enhancing components. Hemorrhagic cysts were diagnosed with pathologic analysis (n=7), follow-up imaging (n=13), or prior ultrasonography (n=5). The presence or absence of T2 shading and T2 dark spots, defined as discrete, well-defined markedly hypo intense foci within the adnexal lesion were recorded. They calculated the following parameters: sensitivity: 36% (95% CI: 19.8, 51.3), specificity: 93% (95% CI: 83.9, 100), positive predictive value (PPV): 89% (95% CI: 63.9, 98.1) and negative predictive value (NPV): 48% (95% CI: 34.8, 61.8) of the T2 dark spot sign for differentiating endometriomas from other hemorrhagic lesions. They conclude that the T2 dark spot sign has high specificity for chronic hemorrhage and is useful to differentiate

endometriomas from hemorrhagic cysts. According to Morisawa et al.,<sup>47</sup> in pregnant subjects the presence of endometriotic cysts with low-height solid component showing high signal intensities on T2-weighted imaging is highly indicative of decidualization and can distinguish endometriomas from ovarian cancers.

**Peritoneal endometriosis:** The diagnosis of peritoneal endometriosis has recently come under discussion for several reasons. In the first place, invisible endometriosis can occur in normal-looking peritoneum.<sup>48,49</sup> Secondly, there is still no convincing evidence that peritoneal endometriosis is per se a progressive disease,<sup>50</sup> and any prospective study is prohibited as long as the diagnosis remains based on laparoscopy. Thirdly, although endometriosis is associated with pain and infertility the clinical significance of peritoneal lesions remains controversial.<sup>51</sup> Under the circumstances, a non-invasive, but reliable diagnosis is a necessity, not only to facilitate and speed-up diagnosis, but also to facilitate progress in our understanding of endometriosis. Indeed, already in 1997, Ayida et al.,<sup>49</sup> had questioned whether routine diagnostic laparoscopy for infertility was justified. They carried out a pilot study assessing in 19 women the use of hystero-salpingo-contrast sonography and MRI as alternatives to laparoscopy and dye insufflations with or without hysteroscopy. They identified 4 cases of stage I and II endometriosis, 3 of stage III and IV disease, including one case of bilateral endometriomas and 1 of hemorrhagic corpus luteum cyst. MRI distinguished the dermoid cysts from the endometriomas, identified the two other cases of moderate-severe endometriosis, but interpreted the hemorrhagic corpus luteum as an endometrioma.

In reviewing imaging techniques for the diagnosis of the condition, Kinkel et al.,<sup>43</sup> concluded that, although ultrasound (US) is able to diagnose most locations, it has limited sensitivity for posterior lesions. On the other hand, MRI has shown high accuracy for both anterior and posterior endometriosis enabling a complete lesion mapping before surgery. It is for this reason that attempts at reaching a non-invasive, but accurate, diagnosis of peritoneal endometriosis have focused on MRI. More than 20 years ago, a Korean Group<sup>52</sup> tried to improve the diagnostic ability of MRI to detect peritoneal endometriosis through fat-suppressed T1-weighted images in 31 patients with laparoscopically-confirmed disease. They found that fat-suppressed imaging provided better diagnostic accuracy (77%) than conventional imaging (55%) ( $p=0.06$ ). Comparative overall sensitivities were 61 and 27%, respectively ( $p<0.01$ ). The “fat-suppression” (FS) methodology was also utilized in another early study in which the technique was used in conjunction with gadolinium-enhanced T1FS and compared to the conventional technique in 21 patients with subsequently proven peritoneal endometriosis.<sup>41</sup> With both techniques ill-defined areas of enhancement were noted in 22 sites throughout the pelvis, corresponding to endometriotic implants seen at surgery in 14 sites. A comparison of sensitivity, specificity, and accuracy for the new and the conventional techniques indicated no significant differences ( $P>0.1$ ).

More recently, two groups attempted to correlate MRI findings in cases of peritoneal disease with laparoscopic observations. A first investigation compared in 44 subjects with clinically suspected endometriosis, pelvic endometriosis staging through MRI to the rASRM classification, following endoscopic diagnosis.<sup>53</sup> Implants were discovered in 20 of 44 patients with MRI and in 23 of 44 with laparoscopy. MRI detected endometrial implants in 76.9% of the cases confirmed by laparoscopy. In terms of staging, they obtained concordance between MRI and laparoscopic classifications in 42

of 44 patients ( $\kappa=0.913$ ) and concluded that, in spite of suboptimal detection of small implants and minor adhesions, MRI may be very useful to guide laparoscopy. The second, similar study evaluated 32 patients in whom at subsequent laparoscopy 143 lesions were identified. US detected 101 and MRI detected 92 lesions.<sup>54</sup> Sensitivity and specificity of the two techniques in recognizing the different locations were 58% and 25%, respectively, for US and 56% and 50%, respectively, for MR imaging. Recto-vaginal lesions were preferentially detected by US, whereas adhesions and cul-de-sac obliteration were more readily detected by MR.

In recent years, US has not been considered to have the potential of demonstrating peritoneal endometriosis and work has concentrated on MRI. In a review of the use of MRI for the diagnosis of peritoneal endometriosis Dunselman and Bees-Tan<sup>55</sup> found 7 studies published between 1989 and 2003 that fulfilled the criteria of methodological quality. Lesions were diagnosed by MRI on the basis of finding abnormal, hyper-intensive foci without mass formation on conventional or T1FS-weighted images and likelihood ratio (LR) was calculated. The values of LR+ and LR- showed that conventional MRI cannot be used to diagnose or exclude peritoneal endometriosis. The poor diagnostic quality of MRI for the diagnosis of superficial endometriosis is most probably related to the small size of implants with different components, including fibrosis, that are difficult to detect on conventional MRI. Recently Thomeer et al.,<sup>56</sup> published preliminary data on results obtained with an optimized 3.0-Tesla MRI protocol showing that this methodology is sensitive and specific enough to detect patients with endometriosis. They prospectively submitted to this technique 40 consecutive patients with clinical suspicion of endometriosis; all subjects subsequently underwent laparoscopic evaluation and all lesions were staged according to the rASRM classification. They calculated a patient-level sensitivity of 42% for stage I (5/12) and 100% for stages II, III and IV (25/25) and a patient-level specificity for all stages of 100% (3/3). The region-level sensitivity and specificity was 63% and 97%, respectively. The sensitivity per lesion was 61% (90% for deep lesions, 48% for superficial lesions and 100% for endometriomas). The detection rate of obliteration of the cul-de-sac was 100% (10/10). They concluded that an optimized 3.0-Tesla MRI protocol can accurately detect the various phenotypes of stage II to stage IV endometriosis.

**Ovarian endometrioma:** Although imaging techniques have the potential of elucidating the complex pathology of the ovarian endometrioma, as already mentioned, it has been documented that the ovarian endometrioma is not like a luteal intra-ovarian cyst, but represents a pseudo-cyst. The pseudo-cyst has two specific features:<sup>57</sup> the stigma of cortex inversion with the adherent endometriotic implant or nodule and the ovarian endometrioma bed. First, at the site of inversion the cortex converges towards the adherent site in the fossa ovarica or latero-posterior wall of the uterus. This is the site where even during careful dissection the endometrioma invariably “ruptures” and spillage occurs. From the endometriotic implant a thin, highly angiogenic endometriotic mucosa extends to colonize the invaginated cortex. The stigma of inversion is not in the plane of the largest diameter at ultrasound, but eccentric at the site of adhesion in the fossa ovarica. Second, the ovarian endometrioma bed is formed by the invaginated inner cortex harboring the primordial follicles and the underlying interstitial and vascular tissue. The one or more locules observed at sonography in the capsule are likely to represent ripening follicles in the inner cortex and are specific for the invaginated cortex. With aging, the ovarian bed shows progressive

smooth muscle metaplasia and extensive fibrosis decreasing the interstitial vascularization. The progressive fibrosis of the cystic wall and the endometrioma bed causes a distinct shrinkage of the endometriotic cavity as seen in the older woman. Therefore, it is of critical importance to diagnose by color Doppler sonography the presence and extent of ovarian devascularization. On the basis of vascular resistance indices Qiu et al.,<sup>58</sup> distinguished four flow grades of cortical devascularization: absent Doppler signal (grade 0 flow), star-shaped signals (grade I flow), stripe-shaped signals (grade II flow) and reticular-shaped signals (grade III flow). If confirmed, the color Doppler sonography findings may have important clinical implications, particularly in adolescents. In the absence of devascularization or the presence of a normal marble-white cortical wall at ovarioscopy surgical excision of the capsule may represent excessive surgery. Muzii et al.,<sup>59</sup> have correctly warned of the risk of excessive surgery of the ovarian endometrioma. Even a large ( $\geq 8$ cm) endometrioma with healthy ovarian cortex can be treated without excision by the two-step reconstructive surgical technique that allows 3 months for the involution of the distended cortex before the reconstructive surgery is performed.<sup>60,61</sup>

**Deep endometriosis:** Over the last years both TVS and MRI have been extensively investigated for the diagnosis of the presence and extent of deep pelvic endometriosis. Since there are no imaging publications on adolescent endometriosis, the present review is by necessity restricted to the major publications on deep endometriosis in adults. The already mentioned study by Chapron et al.,<sup>14</sup> contained an interesting observation: knowledge of adolescent medical and family history can identify markers that are associated with deep endometriosis during surgery. These markers included OC pill use for treating severe primary dysmenorrhea (OR=4.5; 95% CI: 1.9-10.4), duration of OC pill use for severe primary dysmenorrhea (8.4 $\pm$ 4.7 years vs. 5.1 $\pm$ 3.8 years) and OC pill use for severe primary dysmenorrhea before 18 years of age (OR = 4.2; 95% CI: 1.8-10.0). This observation suggests that deep endometriosis in adolescents can be diagnosed at an earlier stage by direct clinical (per vaginam) examination during menstruation and plasma CA-125 concentration as proposed by Koninckx et al.,<sup>62</sup> or by the combination of clinical (per vaginam) examination and transvaginal sonography.<sup>63</sup>

In a pioneering work, Bazot et al.,<sup>64</sup> applied MRI for the preoperative diagnosis of deep endometriosis and the extension of the disease in 195 subjects suspected to have pelvic endometriosis. The MRI diagnosis was histologically confirmed in 83.6% of the patients. The sensitivity, specificity, PPV, NPV and accuracy for deep pelvic endometriosis were 90.3% (93 of 103), 91% (84 of 92), 92.1% (93 of 101), 89% (84 of 94), and 90.8% (177 of 195), respectively. The authors concluded that MR imaging demonstrated a high accuracy in prediction of deep pelvic endometriosis. In the same year Bazot et al.,<sup>65</sup> investigated also the accuracy of TVS for the diagnosis of deep pelvic endometriosis in 142 women with clinical signs of endometriosis. They found a sensitivity, specificity, and PPV and NPV of TVS for the diagnosis of deep pelvic endometriosis were 78.5%, 95.2%, 95.4% and 77.9%, respectively and concluded that TVS accurately diagnoses intestinal and bladder endometriosis, but is less accurate for uterosacral, vaginal and rectovaginal septum involvement. Kinkel et al.,<sup>43</sup> believe that localizations in the utero-sacral ligaments, torus uterinus, vagina and recto-sigmoid can be easily identified by MRI. Posterior locations demonstrate abnormal T2-hypointense, nodules

with occasional T1-hyperintense spots and are easier to identify when peristaltic inhibitors and intravenous contrast media are used.

A comparative study of the relative ability of digital vaginal examination, TVUS and MRI to diagnose recto-sigmoid and retro-cervical involvement was carried out, before laparoscopy, by Abrao et al.,<sup>66</sup> in a total of 104 patients. The presence of endometriotic nodules was histologically confirmed in 94.2% of the patients. They observed that digital vaginal examination had a sensitivity of 72 and 68% and a specificity of 54 and 46%, PPV of 63 and 45%, NPV of 64 and 69% and accuracy of 63 and 55%, respectively for recto-sigmoid and retro-cervical localizations. For TVUS, sensitivity was 98 and 95%, specificity 100 and 98%, PPV 100 and 98%, NPV 98 and 97% and accuracy 99 and 97%. MRI had a sensitivity of 83 and 76%, specificity of 98 and 68%, PPV of 98 and 61%, NPV of 85 and 81% and accuracy of 90 and 71%. In 2010, Busard et al.,<sup>67</sup> reported on the MRI identification of deep endometriosis in 56 patients with known or suspected endometriosis using the value of (MR) diffusion-weight imaging. They identified a total of 112 lesions (62 endometriomas and 48 DIE), 60 of which were large enough to be analyzed through their Apparent Diffusion Coefficient (ADC), concluding that ADC values of deep endometriosis are consistently low, without significant difference between pelvic locations.

A recent systematic review and meta-analysis of ultrasound techniques in the diagnosis of deep endometriosis involving 35 manuscripts eligible for review concluded that TVS should remain the first-line method in the evaluation of patients with suspicion of deep endometriosis.<sup>68</sup> Standard TVS showed specificity greater than 85% for all deep pelvic sites, despite sensitivity ranging between 50% (bladder, vaginal wall and rectovaginal septum) and 84% (recto-sigmoid).

## Endoscopy

Some years ago, Vercellini et al.,<sup>51</sup> assessed the value of diagnostic laparoscopy in the differential diagnosis of chronic pelvic pain in 47 adolescents, 11-19 year old, suffering from cyclic or acyclic pelvic pain of at least six months duration. No pelvic abnormalities were detected in 19 patients (40.4%), endometriosis was detected in 18 (38.3%), partially obstructive genital tract malformations were discovered in 4 (8.4%), and other types of pathology were found in 6 (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 performed before starting a psychiatric evaluation or prescribing long-term medical treatment. Nonetheless, adolescents may not appreciate the abdominal scars of a diagnostic procedure. Today, valid minimally invasive techniques exist to explore the peritoneal cavity of young patients. Back in 1998, Gordts et al.,<sup>69</sup> described as "transvaginal hydro-laparoscopy" a transvaginal needle technique of endoscopy and the same year Watrelot<sup>70</sup> described a similar office procedure, "fertileoscopy", for the investigation of infertility. Both techniques use saline for pelvic distension and can be performed under conscious sedation in an outpatient setting. The transvaginal access with hydro-flotation has the advantage to enable full inspection of the ovaries without the need of manipulation.

In addition, the detection of endometriotic implants and adhesions in the fossa ovarica is facilitated. Also, micro vascularization of the implants is perfectly visible and filmy ovarian adhesions are not



masked by collapse on the ovarian surface. Controlled observations by Brosens et al.,<sup>71</sup> confirmed that by using transvaginal hydro-laparoscopy, distension of the pelvic cavity by saline reveals additional features of peritoneal endometriosis. Indeed, patients with minimal and mild endometriosis and unexplained infertility had significantly more ovarian adhesions on transvaginal hydro-laparoscopy than on standard laparoscopy. The transvaginal needle endoscopy with hydro-flotation allows easy access to the fossa ovarica for the diagnosis of smaller (<4cm) ovarian endometriomas.<sup>72</sup> After aspiration of the chocolate content the cortical surface is inspected for the presence and extent of the thin endometrial-like lining.<sup>73</sup> Treatment of these endometriomas is important, since loss of follicular reserve secondary to cortical fibrosis occurs already in the small endometrioma.<sup>74</sup> Moreover, the inspection of the endometrioma lining at the time of ovariectomy is critical to differentiate luteinized or other ovarian cysts from an endometrioma.<sup>72,75</sup> It can be concluded that for an early and accurate diagnosis of ovarian endometriomas in adolescents, transvaginal needle endoscopy may be preferred over traditional diagnostic laparoscopy because of its easy access to the fossa ovarica and the use of a needle and saline, rather than a scalpel and gas insufflation

## Conclusion

When dealing with early-onset 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 accompanying endometriosis in adolescence and, on the other, to the reluctance of gynecologists to utilize presently-available invasive diagnostic procedures. For this reason, application of the new, non-invasive techniques of TVS and MRI to the identification of the presence of all forms of endometriosis in the adolescent girl seems worth of careful evaluation. Whereas, TVS diagnosis of mild forms of endometriosis in teenagers remains confined to relatively few, ad hoc-trained specialists, various techniques of magnetic resonance seem capable of identifying the presence of endometriosis in its various forms, in a majority of young patients. An early diagnosis is of paramount importance in the presence of an ovarian endometrioma, since in young patients this form has a tendency to progress, endangering the reproductive potential of these young women.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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