

Endometriosis in adolescence

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Abstract

Endometriosis is a chronic disease with endometrial-like tissue located outside the uterus, resulting in inflammation, pelvic pain and infertility. Laparoscopic exploration is the only accurate diagnostic aid for disease recognition, and the time between symptom onset and final diagnosis can be up to 10 years. Endometriosis can already start in adolescence, and in order to make an earlier diagnosis, researchers are beginning to look for an association between specific characteristics, or markers, encountered during adolescence and the later development of the disease.

The purpose of this assignment is to examine the disease mechanism and characteristics of endometriosis, and to review the presumably predictive features during adolescence. The management and effect of treating adolescents with endometriosis will also be discussed.

Some relevant markers for endometriosis are: 1) chronic pelvic pain, cyclic and noncyclic, 2) severe dysmenorrhea, 3) noncontraceptive use of oral contraceptives for dysmenorrhea resistant to NSAIDs and 4) pain interfering with daily living. Being especially alert to these markers, clinical questioning may be one of the most useful tools for identifying girls with endometriosis. Treatment involves NSAIDs, oral contraceptives, surgery, GnRH agonists and mental support. Hopefully, early recognition and treatment in young girls will lead to less extensive surgery and sequelae in adults. However, we still lack strong trials among the adolescent population to prove these hypotheses. Nevertheless, the public and health professionals' knowledge of adolescent endometriosis has to improve, so that affected girls can be taken seriously and not be unnecessarily burdened in a very important phase of life.

Introduction

During the six years of education at the Faculty of Medicine, University of Oslo, all medical students have to write a thesis about a medical topic of their choice. As I consider women's health to be interesting and important, I wanted to find a topic within gynaecology.

My supervisor, Professor in Gynaecology Erik Qvigstad, suggested that I read an article by Dr. Charles Chapron: "Markers of adult endometriosis detectable in adolescence". The article focuses on endometriosis in the adolescent population and that researchers are beginning to see connections between specific characteristics encountered during adolescence and the risk of developing the disease later in life. These markers could be important to make the diagnosis earlier, as it now takes an average of almost 10 years between symptom onset and final diagnosis. I was quickly inspired by the review and was surprised that a disease affecting so many women, is so little known among the actual population the disease involves. Even I was of the opinion that pelvic pain during menstruation is normal and something we females just have to live with.

I found this topic highly relevant and important for my further knowledge on women's health, and therefore decided to use it for my student thesis.

Part I: Endometriosis

Definition and prevalence

Endometriosis is defined as tissue of endometrial-like cells abnormally located outside the uterus. The tissue responds to hormonal changes during the menstrual cycle in a similar way as endometrium inside the uterus. This response leads to a local inflammatory reaction and microscopic cyclical bleeding, giving the affected women pelvic pain, menstrual disturbances and possibly infertility. As an oestrogen-dependent disease, the inflammation will gradually burn out and the intensity of the symptoms will fade, due to lower oestrogen levels after menopause.

Macroscopically, the lesions can be divided into three: superficial peritoneal (and ovarian) endometriosis (SUP), ovarian endometriomas (OMA, cystic-like structures in the ovaries) and deeply infiltrating endometriosis (DIE, deeper tissue infiltration). Based on the total surface size of the lesions, presence of adhesions and ovarian involvement, the lesions are staged as follows (The American Fertility Society, 1985)¹: Stage I minimal, II mild, III moderate and IV severe. The most common locations of involvement are in the cul-de-sac (pouch of Douglas), the uterosacral ligaments and the ovaries. Rarely, endometriosis can be found in distant sites, as the lungs, umbilicus and abdominal scars, for instance caesarean-section scars.

Endometriosis is estimated to affect approximately 10% of women², but as many are asymptomatic, it is probably considerably underdiagnosed³. Up to 40% of women undergoing laparoscopic tubal sterilization, who have already given birth and apparently are asymptomatic, have been found to be affected². 50-60% of women and teenage girls with pelvic pain and up to 50% of women with infertility are diagnosed with the disease⁴. The prevalence of endometriosis worldwide seems to be advancing⁵.

Origin of endometriosis

How the endometrial-like cells end up outside the uterus is still not understood. The traditional theory of reflux menstruation (Sampson 1920) is disputed as the leading candidate². According to the theory, during menstruation, endometrial particles within menstrual fluid flow in a retrograde direction along the Fallopian tubes and are released into the peritoneal cavity. Here, they attach to peritoneal surfaces and proliferate. In order for the cells to survive and grow, the affected women are suggested to have a defect in cell-mediated immunity, which prevents macrophages from clearing the lesions.

Disease at distant sites is thought to have a hematogenous or lymphatic spread aetiology.

As the endometrial-like tissue differs in too many essential ways from the uterine endometrium, many have problems considering endometriosis as an autotransplant². If the Fallopian tubes continue emptying endometrial tissue to the peritoneal cavity during a woman's reproductive life, one would also expect a progressive geographic spread throughout the pelvis as the women age. But endometriosis appears to be positionally static, and most untreated women do not have surgically proven progression of disease². It is also found that 90% of all adult women are regularly exposed to menstrual reflux⁶, suggesting that the process is only temporary normal cytolysis of recently implanted endometrial fragments⁷. At last, the lack of photographic evidence of the initial attachment of refluxed endometrium and additional proliferation, is the most concrete evidence against the theory².

Many now believe that the disease may have an embryological origin². During normal embryogenesis and organogenesis, female pelvic organs follow specific patterned tracts across the posterior coelomic cavity in the embryo. The remnants of these tracts may respond differently to exposure to oestrogen around puberty, and one response could be metaplasia of

mesothelial coelomic cells into endometriotic cells. This may explain why endometriosis does not occur in a random distribution in the pelvis, but rather in a more systematic arrangement². This theory can also explain the cases of endometriosis found in premenarchal girls⁸.

Local inflammatory response

Once implanted, glandular elements of the endometrial-like tissue secrete different paracrine substances that evoke an inflammatory response around the neighbouring tissue⁴.

Proangiogenic substances stimulate local angiogenesis, nerve growth factors promote sprouting of nerve fibres, and proinflammatory cytokines attract and activate macrophages.

Enzymes for tissue remodelling help the endometriotic cells to invade the surrounding tissue, resulting in local fibrosis, adhesions and hemorrhage from the destabilized bordering capillaries. The endometriotic tissue itself does not bleed².

Endometriotic tissue has increased levels of estradiol and prostaglandins, compared with uterine endometrium⁹. Especially increased secretion of prostaglandin E₂, due to local and systemic estradiol stimulation, enhances neuronal invasion and activation of nociceptors (pain receptors) that contribute to persistent inflammatory pain⁴. The endometriotic tissue has a low amount of progesterone receptors and is therefore resistant to the action of the hormone and is inhospitable to embryonic implantation⁴. It seems that progesterone does not have a significant role in the pathogenesis.

Most women will have developed their lifetime load of endometriosis by their early twenties².

At an early stage, the capillaries may not be as notable, giving lesions in teenagers a clear to light pink/red appearance. The tissue becomes darker with advancing age, but that does not mean the disease is spreading².

Symptoms & clinical features

Because of the varying sites of deposits of endometriosis, the clinical features are rather non-specific. A significant share of affected women are asymptomatic, and there has not been found any correlation between the degree of disease and how much women are bothered^{2,4}. The most specific symptoms are pain and infertility. In women undergoing surgery for endometriosis, pelvic pain existed for an average of 6-12 years, with time to diagnosis and treatment being independent of health care system and costs¹⁰.

Pelvic pain is the most common and specific symptom due to endometriosis. Affected women can especially remember dysmenorrhea (painful menstruation) from an early age.

Endometriotic pain during menses is usually referred to as *acquired dysmenorrhea*, while *primary dysmenorrhea* is thought to come from uterine cramping and is not pathological.

Some women can experience both pains at the same time and are capable of separating them from each other². The endometriotic pelvic pain may sometimes start around the time of ovulation and can be mistaken for ovulation pain.

Dependent on the location of the lesions, the endometriotic pain can follow certain patterns. If the uterosacral ligaments or the cul-de-sac are involved, lower back pain and pain on defecation can be present. Endometriotic cyst of the ovaries and periovarian adhesions, due to swelling and tension, may cause pelvic pain to the affected side.

The character of the pain may differ from woman to woman. Some experience the pain continuously throughout the menstrual cycle, others intermittently, with aggravation during the last few days of menstruation or during exercise. The pain can be described as crampy, burning, dull or stabbing. Eventually, the pain may change in character and can worsen in severity. Pelvic pain due to endometriosis is usually chronic (lasting >6 months)⁴, and it may persist at a lower level even during “good” times of the monthly cycle². Up to 70% of women

with pelvic pain resistant to non-steroidal anti-inflammatory drugs (NSAID) or oral contraceptive medical treatment, were found to have endometriosis⁶.

Dyspareunia may occur if the endometriotic deposits involves the cul-du-sac and uterosacral ligaments. These areas are right next to both the end of the rectum and vagina, and physical stimulation of these areas could be painful.

Menstrual disturbances, with heavy or irregular periods or pre-menstrual staining may occur, but are highly non-specific.

Fecundity is decreased in all stages of endometriosis, but only slightly in minimal endometriosis. Women with severe, untreated disease, may become pregnant, though it will take longer to succeed². The direct cause of *infertility* is still uncertain, whether it is the toxic effects of the inflammatory process on the sperm function and embryo survival¹¹ or the anatomical damage and distortion. However, if a couple is having problems conceiving, it is important to also consider the patient's male partner or age-related decline in fertility in both females and males².

Local symptoms caused by endometriosis in distant sites are rare, but could include cyclical rectal bleeding, constipation, diarrhea, haematuria, dysuria, haemoptysis or even epistaxis if the nasal cavity is involved.

Diagnosis

We do not have a good non-invasive diagnostic test for endometriosis⁷. It is also usually difficult to diagnose the disease clinically, as pelvic tenderness is non-specific and the lesions may be small. Endometriosis is the most common cause of pelvic pain in reproductive-age women² and a thorough *pain anamnesis* would then be essential. Blood levels of the tumour marker CA-125 were thought to be useful for the diagnosis, but are now seen as too unspecific and is generally not recommended⁴. Laparoscopy is still the most important diagnostic aid⁷.

Clinical examination, including bimanual palpation, could reveal adnexal masses, thickening or nodularity of the uterosacral ligaments and tenderness in the cul-du-sac. Some would recommend pelvic examination during menstruation to spot lesions, especially in the cul-du-sac, that may not be apparent at other stages of the menstrual cycle. If the examination provokes pain, the patient should be asked if it is the same disturbing pain.

Radiological imaging may be useful in the diagnostic approach. Transvaginal ultrasound and magnetic resonance imaging (MRI) are helpful in detecting gross endometriosis involving the ovaries (endometriomas)⁴. Pelvic MRI may give a complete evaluation of the extent of endometriosis¹³ and is always preferred over computed tomography (CT scan). MRI might especially be useful for identifying DIE lesions, as they will not always be visible from the surface during laparoscopy¹³. However, both MRI and transvaginal ultrasound are of little value in detecting peritoneal and ovarian implants and adhesions⁴, or any smaller lesions because of too little tissue invasion².

Laparoscopy is still the golden standard in detecting endometriotic lesions and to measure the extent of involvement. The lesions can be flat, noduled or cystic, white fibrous, or red, black or yellowish spotted. It may include adhesions to nearby structures, retractions and scarring. One can also often find advanced angiogenesis, with or without haemorrhage. The experience of the laparoscopist is of course relevant for the accuracy of the visual diagnosis. In addition, laparoscopy allows excisions for microscopic diagnostics. When unspecific lesions are observed, biopsies may be taken for definite diagnosis.

Management

Endometriosis is a chronic disease, and there is no absolute cure¹⁴. Medical treatment available today only offers temporary relief of pain symptoms, as it does not eradicate endometriotic tissue or reverse endometriosis-associated infertility. One may remove all visible endometriotic lesions by surgery, but as the cause of the disease is not removed, there are frequent recurrences⁷. Management must therefore be customized for the respective patient dependent on age, symptoms, degree of disease and the patients desire for future pregnancy.

Analgesics, like NSAIDs, which indirectly reduce the formation of prostaglandins, are commonly used to relieve pelvic pain and dysmenorrhea, but has no effect on the disease. For many patients NSAIDs are not enough for symptom relief, and oral contraceptives are used in addition.

Hormonal treatment is effective to suppress and reduce oestrogen synthesis and release. The hormonal effects and menstruation are put on hold (amenorrhea), thus suppressing further growth of endometriotic tissue and subsequent fibrosis. The treatment has no impact on fecundity in any way. The hormonal treatments include gonadotrophin-releasing hormone

(GnRH) agonists, gestrinone, progestin and danazol. GnRH agonists are found highly effective in the management of endometriosis¹⁵, and are the most widely prescribed medicine for treating symptoms². As GnRH agonists have considerable side effects, including a hypoestrogenic state with loss of bone mineral density, vaginal dryness etc., add-back therapies (oestrogen or oestrogen/progestins) are recommended in addition. The clinical use of danazol, much used earlier, is now very limited due to its androgenic side effects (acne, hirsutism and deepening of voice), some irreversible⁴.

Surgical treatment is the treatment of choice for most patients with severe symptoms, progressive disease and in some cases of endometriosis-associated infertility. Small lesions can be treated by laser ablation or diathermy under laparoscopic vision. Laparoscopic ablation improves symptoms and increases conception rates⁹. Endometriotic cyst should be drained and the inner lining excised, but if the patient desires children, the surgeon should conserve as much ovarian tissue as possible. If the patients family is complete, total hysterectomy and bilateral oophorectomy may be appropriate⁹.

Excision of endometriosis is associated with impressive and long-lasting symptom reduction and quality of life improvement². But if surgery is done early in the process or is performed by an inexperienced surgeon, some lesion may escape excision as the age-advancing colorization has still not occurred or is not recognised. The patient would then require subsequent operations. The reported recurrence rate is an estimated 20% at 2 years and 40-50% at 5 years⁷. It seems like the early stages of disease show the least pain improvement with surgery (38% after 6 months), while the late stages are most improved (100% after 6 months)¹⁵.

Associated diseases

There seems to be a relation between endometriosis and autoimmune and endocrine disorders and certain cancers^{11,12}. Compared to the general female population, women with endometriosis have a greater risk for lupus erythematosus, Sjögrens syndrome, rheumatoid arthritis, multiple sclerosis, hypothyroidism, chronic fatigue syndrome and fibromyalgia. Atopic diseases such as allergies, asthma and eczema are also more common. Among the cancers, affected women and their families, are at a greater risk for developing breast cancer, melanoma, ovarian cancer and lymphoma (Non-Hodgkins). These associated diseases could indicate that a defect in the immune system plays an important role in the pathogenesis of endometriosis.

Part II: Endometriosis in adolescence

Endometriosis was thought to be a disease affecting just adult women, but is now increasingly recognised in adolescent girls as well^{8,15}. The majority of patients with surgically diagnosed endometriosis report symptoms already from adolescence¹⁰, and there is an increasing number of reports in the literature of endometriosis arising in young patients around menarche³.

Comparative data (1980-1998) gathered for the US Endometriosis Association show that girls experiencing their first pelvic symptoms are younger than before, and that the course of the disease seems to be more severe with an earlier age of onset¹². Those who were youngest at symptom debut were most likely to be periodically unable to carry on normal activities, including work or school. The number of young women dropping out of college or high school due to endometriosis seems also to be increasing¹².

The search for markers for an earlier diagnosis

Symptoms of endometriosis have most likely burdened the women and immediate family for years before diagnosis. The economic burden is also considerable because of repeated absenteeism from work and school, numerous medical treatments and eventually extensive surgery¹⁰. With the lack of a non-invasive diagnostic test, researchers have studied the history of symptoms and the clinical factors present in adolescence, looking for similarities or markers that could predict which girls will develop endometriosis and which are most likely to benefit from surgical exploration and an earlier diagnosis¹³.

Pelvic pain and dysmenorrhea

The relationship between chronic pelvic pain symptoms and endometriosis is widely accepted¹⁶. More than half of women with pelvic pain are diagnosed with endometriosis^{4,16}.

Dysmenorrhea affects 70-90% of all adolescent and young adult females¹³, but case-control and correlation studies clearly indicate an association between severe dysmenorrhea and endometriosis¹⁶. Treloar *et al.* (2010) found that women with a history of dysmenorrhea are more likely to develop endometriosis than women never or seldom experiencing pain during menstruation¹⁷. They also found a significant trend for increasing risk of endometriosis with an increasing frequency of menstrual associated pain. Pelvic pain during ovulation was not found relevant.

In Fauconnier *et al.*'s review (2005) of the relationship between pelvic pain and endometriosis, the association was not specific for the macroscopic type of the endometriotic lesions or their anatomical locations¹⁶. The exception was posterior DIE, where two signs could be useful for the preoperativ diagnosis: severe dyspareunia and painful defecation during menstruation.

Other studies have also found that patients with DIE report more painful symptoms compared to patients with endometriosis without DIE. Chapron *et al.* (2011a) showed that patients with DIE lesions had a significantly higher incidence of complaints for pelvic pain (intensity and duration), dysmenorrhea (primary and secondary) and deep dyspareunia¹⁰. To grade the interference with activities of daily living, they found that absenteeism from school during menstruation was greater in girls who were later found to have DIE lesions compared to those with "just" SUP and/or OMA.

As earlier stated, there has not been found any correlation between the stage of disease and the amount of pain the women are experiencing. However, it has been demonstrated that the endometriotic lesions most commonly observed in adolescents, clear and red, are the most painful, compared to the black, brown or powder burn lesions mainly seen in adults¹⁴. In addition, a majority of adolescents also describe noncyclic pelvic pain, and not just dysmenorrhea (cyclic pain) which is traditionally considered the classical symptom in adults^{6,8}. This is important to have in mind when evaluating pelvic pain symptoms in young women.

Therefore, analyses of the pain-related symptoms may be useful for the preoperative diagnosis of endometriosis and severe dysmenorrhea deserves to be tested as a screening tool¹⁶.

Chronic pelvic pain not responding to conventional therapy

In the late 1990's, Laufer *et al.* (1997) presented their results of a study evaluating adolescent girls with chronic pelvic pain non-responsive to conventional medical therapy⁶. The study included 46 girls between the age of 13-21 years with chronic pelvic pain lasting for more than 3 months, and not responding to a regime of an NSAID and a cyclic low-dose combination oestrogen/progestin oral contraceptive pill. They were evaluated for endometriosis on the basis of either visual image of gross lesions by laparoscopy, or histologically with random pelvic peritoneal biopsy samples. They found that 32 of the girls (69,6%) had endometriosis, and only one of them had lesions not visible by laparoscopy.

Reese *et al.* (1996) showed similar results: a 73% incidence of endometriosis in adolescents not responding to medical therapy⁶. Thus, it may be concluded that about 70% of adolescents with chronic pelvic pain resistant to NSAIDs and cyclic oral contraceptive pills, are likely to suffer from endometriosis.

Noncontraceptive use of oral contraceptives for dysmenorrhea

The potential association between oral contraceptives (OCs) and endometriosis has been confusing; some researchers have found an increased risk of endometriosis when using OCs, some a lower risk, while others have not found any link at all¹⁹. Knowing the relationship between OC use and endometriosis would be very valuable, considering the high frequency of OC use in adolescence and the increasing prevalence of endometriosis worldwide¹⁸.

Vercellini *et al*'s (2010) thorough systematic review and meta-analysis may have gotten us one step closer to an explanation¹⁸. Analysis of 18, studies selected from 608 potentially relevant ones, showed that OCs appear to decrease the risk of endometriosis in current users, while potentially increasing it in previous users. Although there is a significant difference, they still cannot conclude that past OC use promotes future development of the disease. Current use could just temporarily reduce the pain symptoms, thereby delaying further diagnosis. Therefore, they requested future studies to include why the patients start with OCs in the first place.

Chapron *et al.* (2011b) confronted in a cross-sectional study with 566 patients various characteristics of OC use, - ever or never used, past or current, age at prescription, duration and so on - among women with endometriosis, compared to a control group without endometriosis¹⁹. The surgical diagnosis of endometriosis in the study group was further categorised by their worst lesion as SUP, OMA and DIE. Their data showed that ever OC users, both past and current, had an increased incidence of endometriosis compared with women who had never used OCs. And as Vercellini *et al.*, they found no increased prevalence of the disease among current OC users. But in addition, the researchers found that women who had previously used OCs for severe primary dysmenorrhea had an even greater risk of

being diagnosed with endometriosis later in life. The association with DIE was especially evident. There was also an increased risk of endometriosis with previous OC users for other reasons than primary dysmenorrhea, such as secondary dysmenorrhea, menstrual disorders and contraception, but to a lesser extent. Furthermore, the age at which OCs were prescribed and duration of OC use did not seem to be of any relevance.

Chapron *et al.* (2011a) found the same association in another study, where the use of OCs when prescribed for severe primary dysmenorrhea, was more frequent in women with DIE lesions¹⁰. In this group, OCs were also prescribed at a younger age (<18 years) and for a longer time, compared to the controls.

The authors from both studies stress the fact that their results still do not imply that past OC use increases the risk of endometriosis, or that current use offers proven protection against the development of endometriosis and especially DIE^{10,18,19}. For example, if women at risk for endometriosis are more likely to start with OCs, a selection bias could explain the results. However, the authors do agree that past use of OCs for primary dysmenorrhea may serve as a marker for women who are more prone to develop the disease later in life^{10,19}.

Age of menarche and other menstrual characteristics

The first systematic review of the potential relationship between age of menarche and increased risk for endometriosis, was published by Nnoaham *et al.* in 2012²⁰. Only published case-control studies which compared age at menarche in women with surgically confirmed endometriosis to those unaffected, were included. Early age at the first period was defined as up to and including 12 years. Because of the considerable differences between the studies, their results could be due to chance alone and the meta-analysis showed no statistically

significant increase in risk between the cases and controls. However, when the meta-analysis was restricted to studies with a higher control quality for potential confounders, the heterogeneity was eliminated. The results then showed a probability of 55% (a small increased risk), that a woman with endometriosis was younger at menarche than a woman without endometriosis if both individuals were chosen randomly from a population²⁰. In addition, the size and significance of the association were greater in studies of women with moderate-to-severe disease (stages III-IV) compared to studies of minimal-to-mild disease (stages I-II), carefully implying that early menarche may be linked with the risk of moderate-to-severe endometriosis.

Treloar et al. (2010) went further to examine the relationship between adolescent or early menstrual characteristics before symptom onset, and later diagnosis of endometriosis¹⁷. They studied the age of menarche, lengths of menstrual cycle and the heaviness of menstrual flow in 268 Australian women. In addition, they registered tampon use and sexual intercourse during menstruation, which both could expect to lead to retention of blood flow and increase the potential retrograde flow of menstruation to the peritoneum. Their results implied that menarche after the age of 14 was strongly and inversely correlated with endometriosis. Neither heaviness of flow, duration of natural menstruation or shorter menstrual cycle (thereby more cycles), were found to be significantly related. The use of tampons, even by night, or sexual intercourse during menstruation were also not significant for disease development.

Based on these studies, a history of earlier age at menarche may be used as a marker to guide diagnosis if other symptoms point to endometriosis, especially if suspecting moderate-to-

severe disease^{17,20}. Menarche later than 14 years may suggest other differential diagnosis if endometriosis-related symptoms are absent^{17,20}.

Genetic predisposition

Familial aggregation of endometriosis has been reported since the 1940s and -50s^{5,13}, but formal family studies were not carried out until the 80's⁵. Simpson *et al.* (1980) reported that the risk for first degree relatives of women with severe endometriosis was six times higher than that for relatives of unaffected women¹¹. However, most family studies, including Simpson *et al.*, show inadequate study designs and statistical analysis⁵. Problems are too small sample sizes, not adjusting for familial aggregation of confounding risk factors, such as age at menarche, and sharing of environmental risk factors as well as not reporting how many sisters that cases and controls have. In Di and Guo's review (2007) evaluating the evidence for a hereditary factor in endometriosis⁵, the authors conclude that considering the broad range of symptoms and variable age of onset, it is unlikely that a single or a few genetic polymorphisms would completely influence the predisposition to the disease. They rather suggest that the rising prevalence of endometriosis worldwide might be a "maladaptation to dramatically changed life-style and environment (such as earlier onset of menarche and delaying childbearing)".

On the other hand, the authors of Montgomery *et al.*'s review (2008), which summarises gene mapping studies in endometriosis, believe that current gathered evidence supports a genetic contribution to the risk of endometriosis¹, and point out especially two studies. In an extensive classical twin study in Australia (1999), the researchers found that genetic factors contributed with about half of the variation in endometriosis risk, even when adjusted for the potential contribution of increased sharing of environmental risk factors among identical versus non-

identical twins. In a thorough analysis of endometriosis cases in an large Icelandic population (2002) that was controlled for bias in various ways, the authors concluded that there was evidence for genetic effects in every case. Later, Borghese *et al.* (2008-2010) achieved robust results demonstrating specific gene expression and methylation profiles fitting to each category of the endometriotic disease, by sorting between superficial and deep lesions¹³.

One may conclude that there is evidence for a genetic contribution to the risk of developing endometriosis¹ and that early screening in young patients with a positive family history could be useful, but not used alone, to select the girls who might best benefit from early surgical exploration¹³. However, stronger study designs are desired and these should involve replication studies with thousands of cases and controls¹.

Summary of potential markers

With the lack of non-invasive diagnostic tests, symptoms presented at the time of adolescence is probably the most confident predictor of who is at greater risk of developing endometriosis, particularly DIE, later in life¹³. Isolated, the markers are rather unspecific, but the physician can be alerted of an increased endometriosis risk by combining the markers in a thorough anamnesis.

Table 1 summarises the set of markers that researchers so far believe are of value to identify young girls who already have or are likely to develop endometriosis.

Part III: Dealing with adolescent endometriosis

The late diagnosis

The late final diagnosis of endometriosis may have many explanations. Only recently there is an increasing awareness that endometriosis can start already at adolescence. As well, the most specific symptom of the disease, dysmenorrhea/pain, is so widespread that it is unfortunately seen as a normal part of being a fertile women by both physicians and girls. The US Endometriosis Association¹² report a 9,28 years delay between the onset of symptoms and diagnosis, with the affected girls waiting on average up to 5 years before seeking a doctor for help. 52% of the girls were then told by their family doctor, and 69% by their gynaecologist, that “nothing was wrong”. An interesting finding was that reproductive endocrinologists and emergency doctors, compared to gynaecologists and family practitioners, used half the time to diagnose the disease (respectively 1.4 and 1.7 years compared to 4.1 and 5.3 years). Chronic pelvic pain is also frequently managed without consulting a gynaecologist¹⁰.

It is obvious that both patient’s delay and doctor’s delay should and can be considerably reduced. Myths and misconceptions about menstruation and pelvic pain have to be replaced with modern, up-to-date knowledge among health professionals and the public. Especially family doctors, pediatricians, school nurses, gym teachers etc. in contact with adolescent girls and their parents must be aware of adolescent endometriosis, so that the girls can be taken seriously. Chronic pelvic pain is not normal, and there is no need for them to wait so many years until contacting a doctor. The girls should then be referred to physicians with special interest and competence in adolescent gynaecology.

Fortunately, more women are becoming aware of the existence of endometriosis, and countries like Italy (2007) are supporting promotional campaigns in the media to increase disease awareness and the need for an early diagnosis⁷.

Management of adolescent endometriosis

At the first contact with girls with cyclical/noncyclical pelvic pain, their complaints should be thoroughly explored. As over 50% of girls with pelvic pain eventually end up being diagnosed with endometriosis, one should start screening the girls for markers for endometriotic disease. An anamnesis is cheap, effective, and most importantly, can promote a good trusting doctor-patient relationship, giving the young girl the feeling that she is understood and being taken care of.

Questions that could be a part of a standardised questionnaire to ask girls and women with pelvic pain are summarised in table 2. For young girls, answering the questions with help from for example a school nurse or doctor's secretary, could be beneficial before their first consultation with a doctor.

It is important to reassure the young girls that a gynaecologic examination is not required for the diagnostic investigation or treatment of their pelvic pain^{15,21}. An internal physical examination can be challenging in adolescents and the usual bimanual approach may not be possible. However, it is important to rule out any vaginal obstructive anomalies, but this can easily be done by inserting a Q-tip into the vaginal canal, to ensure that it goes to an adequate length¹⁵. Ovarian masses or congenital anomaly of the reproductive tract could also be detected with a pelvic ultrasound¹⁵ or MRI.

Initial therapy for dysmenorrhea is NSAIDs and *cyclical* combined oral contraceptive pills. This regime should be tried out for 2-3 cycles/months in adolescents, compared to 6 months in adults¹⁴. During these months, it could be useful to record the development of symptoms in

a pain diary. If the girl is still experiencing pain during this period, and if she feels that the pain is limiting her daily living, further examinations should be done.

The American Congress of Obstetricians and Gynecologists (ACOG) Committee Opinion on Adolescent Endometriosis, recommends the use of laparoscopy for the definitive diagnosis of endometriosis in adolescents¹⁴. Ultrasound and MRI is not very helpful to detect or see the extent of the disease in these patients, as most adolescents have stage I or II disease^{8,14}, and endometriomas are rare in this group¹⁴. However, these could rule out other disorders, for example a reproductive tract anomaly. If the patient is over 18 years and can decide for herself, one could make the diagnosis without laparoscopy, by determining if her symptoms improve with a trial of GnRH agonist therapy¹⁵. However, for younger girls (<18 years), empiric testing is withheld due to the unfortunate effect of GnRH agonists on the bone mineralization occurring during adolescence. Most parents would also prefer a definitive diagnosis before starting their daughters on medication¹⁴. Therefore, a laparoscopy for visualisation and biopsy should be offered as a final diagnosis for the younger girls.

When performing the diagnostic laparoscopy, the surgeon has to be prepared to destroy all visible endometriotic tissue during the same session. If the surgeon is not confident in identifying the atypical lesions in adolescents, or does not have enough experience in destroying or removing them, the patient should be referred. Unfortunately, there are no published data on the outcome of surgical therapy for adolescent endometriosis, but as symptoms generally return in the majority of adult patients after one year without further treatment, surgery alone is not considered adequate treatment for adolescents²¹.

Hysterectomy is not appropriate for an adolescent population¹⁵.

All patients should after therapeutic laparoscopy be placed on suppressive therapy to inhibit recurrence and progression of symptoms¹⁴, until they desire children²¹. The first-line treatment for adolescent endometriosis is currently *continuous* administration of oral contraceptives, usually combined oestrogen/progestins¹⁵. The girl has to take one pill daily without breaks or “sugar pills”, compared to contraceptive use. To prevent breakthrough bleeding, a long-cycling regime where the girl is off the pills one week every 3-4 months, is then preferred. The resulting menstruation could be painful, but could also give a reassuring feeling of normality. The benefits of progestin-only therapy are uncertain^{14,15,21}. Danazol is not recommended for adolescents because of the androgenic side effects¹⁴.

If the girl still does not respond satisfactorily and if she is 16 years old or older, one should start with the highly effective GnRH agonist therapy¹⁴. Because of the unfavourable effect on permanent bone density (therefor the age limit), GnRH should always be prescribed with add-back therapy (oestrogen or oestrogen/progestin) which reduces the bone loss, without stimulating the endometriotic lesions¹⁴. The adolescents should also take calcium and vitamin D supplements in addition to the GnRH and add-back therapy regime, and a bone density test should be obtained every two years¹⁴. To avoid any potential problems with the use of GnRH agonist in adolescents, it is important to educate the girls about possible side effects¹⁵. The regime is usually tried for 3-6 months, eventually followed by OCs, often in the long-cycling fashion with 3-4 periods yearly.

The girls well-being is important, and educational materials could help them to better cope with their chronic disease¹⁵. A structured life, with regular exercise, healthy diet, moderate alcohol intake and no smoking, is encouraged. For affected adolescents, meeting others with

the same condition, for example through teen peer support programs and/or Internet chat rooms, are found to be helpful and should be available¹⁵.

Treating endometriosis in adolescence – Does it make a difference?

We can all agree that it is important to diagnose endometriosis as quickly as possible to reduce young girls pain symptoms and to improve their quality of life. But would early surgical intervention in teenagers reduce the need for extensive surgery as grown ups and limit disease sequelae in the future? In adults the severe forms of the disease, DIE and ovarian endometriomas, often lead to mutilating surgery, and the patients may suffer from persistent symptoms due to removal of gastrointestinal tract segments, an aggravation of infertility and/or have reduced ability to respond to assisted reproductive therapies¹³.

Unfortunately, with the limited data on adolescent endometriosis, one cannot yet confirm that intervening in the adolescent population prevents long-term sequelae such as pain and infertility as adults⁸. However, there is reason to believe that an earlier diagnosis of endometriosis would result in less extensive surgery, although this is not yet proven¹³. More data from the adolescent population, with long-term follow-up studies of disease progression and quality of life with medical versus surgical treatment, are necessary⁸. Nevertheless, the affected adolescent girls deserve to be taken seriously and followed closely for eventual recurrences and future pregnancy wishes.

Conclusion

Endometriosis, previously thought to occur only in adult women, is finally starting to be recognised as a condition that can develop already during adolescence. Researchers have now found that adolescents with certain characteristics, or markers, for example severe dysmenorrhea, OCs used for dysmenorrhea resistant to NSAIDs and dysmenorrhea interfering with daily activities, have a higher risk of developing the disease later in life. Being especially alert to these markers, clinical questioning may be one of the most useful tools to identify girls who are most likely to benefit from early diagnosis and surgical intervention. It is still uncertain if early surgical and medical treatment retard future disease development with its sequelae, due to the lack of strong, well-designed trials among affected young girls. Nevertheless, the public and health professionals' knowledge of adolescent endometriosis has to improve, so that affected girls can be taken seriously and not be unnecessarily burdened in a very important phase of life. Fortunately, the interest for endometriosis in adolescence is rising internationally and hopefully more countries, including Norway, will contribute to the research of the disease in this population, which still has too many questions unanswered.

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Appendix

Table 1: Symptoms and markers at adolescence predicting the risk of development of endometriosis	
Chronic pelvic pain, cyclic and/or noncyclic	
Severe primary dysmenorrhea	
Noncontraceptive use of oral contraceptives for dysmenorrhea	
Dysmenorrhea resistant to NSAIDs and/or oral contraceptives	
Interference of daily living during menstruation, e.g. absenteeism from school	
Dyspareunia and/or pain on defecation during menstruation	
Early age of menarche (≤ 12 years) (but not after 14 years)	
Family history of endometriosis	

Table 2: Pelvic pain – endometriosis?**Pain anamnesis**

- a) When did you first experience the pain? (Age, year)
- b) When does the pain come? Independent, before, during (first or last days) or after menstruation?
- c) Where is the pain? Symmetrical or unilateral?
Radiation?
Lower back pain?
- d) Quality and characteristics of pain? Burning, dull, stabbing?
Continuous, cramping with intervals?
Intensity of pain? (Grade between 0-10)
Changes in intensity during the painful period?
- e) How long does the pain last?
- f) Does anything make the pain better? Lying still, moving around?
Heat, cooling (water bottle, shower)?
Paracetamol, Ibuprofen, NSAIDs (e.g. Naproxen) etc.?
- g) Does anything make the pain worse? Movement, exercise?
- h) Does the pain affect your daily living? Participation in school, sports, social events?
- i) How does the pain make you feel? Disadvantaged compared to others at the same age?
Affecting your quality of life?

Period anamnesis

- a) When did you have your first period?
i) <12 years ii) 12-14 years iii) >14 years
Accurate time (if remembered): (Month, Year)
- b) How many days does an average period last?
- c) How many days between each period?
- d) Little, average or heavy flow? Staining clothes? Dizziness or fainting during menstruation?

Other symptoms/complaints

- a) Does inserting/using tampons during menstruation feel uncomfortable/hurt? Yes No

If yes: Location?		
b) Pain on defecation?	Yes	No
If yes: Location? Associated menstruation?		
c) Pain during sex (if sexually active)?	Yes	No
If yes: Location? Associated menstruation?		
d) Constipation, diarrhoea?	Yes	No
e) Painful urination, blood in urine?	Yes	No
Family history		
a) Family members with (maternal and paternal):		
i) Pelvic pain / Pain during menstruation?		
ii) Problems getting pregnant?		
b) Atopic profile: allergies, asthma or eczema?		
c) Endocrinologic or autoimmune disorders (lupus erythematosus, Sjögrens syndrome, rheumatoid arthritis, multiple sclerosis, hypothyroidism, chronic fatigue syndrome, fibromyalgia)?		
d) Cancer (breast cancer, melanoma, ovarian cancer, Non-Hodgkins lymphoma)?		