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Endometriosis in Adolescents that Deserve Attention, not just Compassion: A Review Article

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Abstract
Today endometriosis is not an uncommon gynecological disease. Endometriosis can be known by the existence of endometrial gland and stroma tissue anywhere external from the uterus. Some of its characteristic features are inflammation, chronicity, and hormone (estrogen) dependency. It is the cause of pelvic pain and infertility in about 10% of common people. It is found usually adhered to the pelvic peritoneum. The onset of pain can take place even prior to the immense of the menstruation which is the most often encountered symptom by adolescents although multiple symptoms experienced by the individual at a same or different interval. Laparoscopy is used for diagnosis of endometriosis which is invading procedure and economically costly so, it might be the reason for the delay in diagnosis. Until when destructive lesions may complicate the reproductive organs in a female and further compromise the fertility of the patient. Adolescents' endometriosis may differ from that of an adult female in terms of presentations and anatomical features of the lesions itself. Multiple reasons contribute to this undeniable difficulty in the diagnosis and underestimation of the problem and what appears may just be the tip of an iceberg. In this review, we have tried to understand the disease in this specific population comparing different studies both old and new.
Keywords: Endometriosis, adolescents, pathogenesis, adult, laparoscopy.

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1. Introduction

Endometriosis is a chronic disease, that is under-diagnosed, under-reported, and under-researched [1]. It is one of the most prevalent diseases in Gynecology that is defined by the presence of endometrial tissue (both gland and stroma) anywhere outside the uterus. Previously, endometriosis had been thought to occur only rarely in adolescence, but with an increasing awareness of the disease among the medical fraternity, researchers and the patient's consciousness, it is being diagnosed more frequently [67]. Painful menstruation and pelvic pain are usually seen as the cardinal symptoms in adolescents. Previous studies have shown that twenty-five to about forty percent of the teenage female with chronic pelvic pain has endometriosis [2,3]. Although endometriosis was first described more than 150 years ago, the exact causes are still unclear [68]. Different hypothesis and theories have been put forward to describe the occurrence of the disease due to which it's sometimes referred as "disease of theories" however genetic pre-disposition is now developing and focus has been given on modification or genetic mutations that may begin in utero or in teenage and young adults [4].

Hence, this review will discuss overall complexities and general condition of endometriosis in adolescents to understand why it is difficult to trace, diagnose and manage them in this vulnerable age group, comparing different studies both old and new.

2. Epidemiology

After several years of research very little is understood up to now about the actual and true nature, incidence in the general population and its risk factor, so it is regarded as the mysterious disease. No doubt there may be numerous factors that may have been contributed for difficult in tracing epidemiology of the disease that is challenging and tough to address. For example, controversy in the definition itself especially one that of adolescents, selection of the control group and other methodological problem's etc. However, previous few decades have shown fruitful result regarding the epidemiology of endometriosis after dedicated studies and hard efforts. But, still, it seems we are far from the actual incidence, especially in adolescents because of the lack of un-uniformity among various studies put forth [5]. A forty percentage of incidence

rate was reported by Goldstein et al. [6] in female adolescent those undergoing laparoscopic surgery for chronic pelvic pain(CPP) and Laufer et al. [7] found sixty-seven percent of endometriosis diagnosed at the time of surgery having refractory pain common to medical management like Nonsteroidal anti-inflammatory Drugs(NSAIDs) or Oral Contraceptive Pills(OCPs), while in another study seventy-five of adult women diagnosed with endometriosis reported that their symptoms started before age twenty [64]. However, it must be known that estimates of endometriosis in a clinical population may vary by different studies and the criteria taken for the diagnosis.Yet other systemic studies (of 15 studies combined) showed the prevalence of visually confirmed endometriosis sixty-two percentage in a whole population of adolescent girls who underwent keyhole investigation, in an individual unresponsive to therapy for CPP seventy-five percentage, in individual with menstrual pain seventy percent and forty-nine percent in girls with CPP that is not necessarily resistant to treatment [65]. While the American Society for Reproductive Medicine(ASRM) claimed the endometriosis among the adolescent girls to be thirty-two percent in general, in CPP resistant to therapy sixteen percent, in the individual with menstrual pain twenty-nine percent and in individual with CPP fifty-seven percent that was not necessarily resistant to any treatment. The quality of research done may influence an overestimation of the prevalence in the given population. Thus, estimates of endometriosis in a clinical population may vary by different studies and the criteria taken for the diagnosis.

2. Etiology

Multiple theories and concept have been put forward up till the date explain the nature and origin of the disease, however, its clinical signs and symptoms cannot be explained and understood relying on the individual one. Among the theories that have been postulated for the origin of the disease, for example, the theory of transplantation or implantation (also called the theory of retrograde menstruation), by Sampson,1921, metaplastic theory by inflammation, by Hueter, 1918, the metaplastic by hormonal (also called metaplasia, by Novak,1931) , a theory of oxidative stress and inflammation, immune dysfunction, apoptosis suppression, genetic and stem cells, environment, autoimmune etc. [63] but among them five that best explains the pathogenesis especially, in adolescents are: (1)The genetic theory-" endometriosis is probably familial as a complex inherited attribute since, among first-degree relatives of affected females, the prevalence of the disease is six to nine times higher than the general population" [8]. The theory is backed by numerous literature [9-13]. (2)Theory of Mullarian rests talk of the origin of the disease due to the seeding of endometrial tissues during the fetus development that gets stimulated by ovarian hormone at the time of menarche [14-16]. (3)The transplantation theory: blood flow from the uterus may flow in an opposite direction through a fallopian tube and along with it endometrial tissue may get implanted in the abdominal viscera [17,18], in female having poor immunity [19], in a female with environmental toxin's exposure, teenager's having outlet obstruction because of congenital defect [20,21], and in teenagers after post-surgical repair of inborn defects which favors resorption of endometriosis [22]. The vulvar wound has also been found with endometrium tissue which may be due to the shedding of endometrial along with the normal menstrual cycle [23]. (4)The coelomic metaplasia theory [24,25]. (5)Endometrial tissue has been transplanted mistakenly during surgeries like C-section, hysterotomy (vaginal and abdominal) and episiotomy [26,27]. A hematogenous and lymphatic spread is usually rare. No individual theory can justify every case of endometriosis, particularly related to adolescents. Postpubertal and premenarcheal endometriosis are the most difficult cases [28]. Multifactor causation with varying mechanism could give rise to the disease itself.

3. Presentation

3.1 The disease begins in adolescents

The females in the childbearing age group are the major targets of the disease and are generally concerned with pain and infertility. But, the undeniable fact is that the substantial number of studies shows evidence of the disease beginning in adolescents. There may be a difference between the adult and adolescents symptomatologically while presenting to the clinician. So, the attending physician must consider endometriosis in this age group as their differential diagnosis in individuals who so complain of menstrual and pelvic pain to avoid delays in diagnosis and management as growing numbers of studies have confirmed all the stages (1-4) of the disease [59,60,61] in adolescents.

"38% of women with endometriosis had symptoms beginning before 15 years of age and when this happened an average of 4.2 physician consultations was required before a diagnosis was reached, more than in any other age group [29]." says the

Endometriosis Association record. Time plays a vital role in getting essential and appropriate suggestions and treatment from physicians. So, to safeguard the health of teenagers, without delay the individual must be referred whenever the confusion arises(especially of the physician skills and knowledge) and lack of facilities like unavailability of laparoscopist and laparoscope etc. The unbearable pain perceived by the patients usually is taken as of primary menstrual origin both from the guardian, the general physician and considered as a normal variant of the female child leading to delay in an initial diagnosis of the disease in adolescents. Much awareness and proper management are required and not just compassion whenever dealing with such individual child who misses their basic day to day activities like going to school and lags behind in their other general activities and complains of pelvic pain.

3.2 Symptoms may differ from adults

Endometriosis being the most common cause of secondary dysmenorrhea [7,66,30] it must be given a second thought, especially when confronting patients who have tried NSAIDs and OCPs as primary therapy. The statistic shows the disease occurred about eleven percent in an individual with inborn anomalies of the reproductive tract [31,32] while up to seventy-six percent was thought in the patient with Müllerian abnormality and obstruction of the tract [33]. Bowel symptoms like rectal bleeding, constipation, painful defecation etc. that may be cyclic and bladder symptoms like dysuria, urgency, hematuria etc. were also found frequently [34]. Ovary and uterosacral involvement were comparatively scarce before twenty-five years of age. While unlike adults, adolescents tend to have both cyclic and acyclic pain but some claim the presence of acyclic CPP that is not responding to the primary medical management in teenagers are appropriate for undergoing diagnostic laparoscopy [35] because while presenting, this group of individuals for the obvious reason many not be sexually active and may rarely seek help for fertility, they are not yet conscious of childbearing and dyspareunia many not be part of their concern.

Diagnosis

4.1 History, diary and questionnaire may be helpful

The diagnostic procedure is not different in adolescents that from adults suffering from endometriosis. No doubt, initially clinical history plays a vital role in addressing the unbearable pain that may be related to bowel and bladder or both which may be resistant to painkillers. A pain diary, suggested by M. R. Laufer et al. [36] can help the physicians understanding the nature and type of pain. One can also get help from the various questionnaire and screening tool designed specifically to address this age group so that there may be less chance of missing any important and specific piece of information, for example, HEADSS [37] is a specific type of questionnaire designed for adolescents for this purpose answering which they feel comfortable are more open with increased willingness. Isolation, confidentiality, and vulnerability of this age group are to be carefully maintained and proper care should be taken when necessary, an appropriate counseling should be practiced from the very initial visit, explaining the actual scenario and its consequences to both the patient and the family.

4.2 Keyhole surgery-the gold standard

There are various approach and methods that may aid in diagnosing and confirm the endometriosis in the female but no one can deny that keyhole surgery is the best and the most suitable one for various reasons. The biopsy can be obtained by the surgeon by visually seeing the lesions in the abdominal organs. The biopsy is then confirmed the presence of the disease via the laboratory. That is why the method is also called the gold standard method. Sophisticated and advanced techniques of imaging, for example, ultrasonography, computed tomography(CT), magnetic resonance imaging(MRI) may be of some help in diagnosing less invasive endometriosis but due to the high cost of the later, accessibility is scarce. Endometriosis is a hereditary disease and runs in a family so comprehensive family history could be the turning point in the diagnosis of the disease. The incidence of an individual having a positive family history was about seven percent while only two percent were found in control groups [38]. Similarly, the adequate physical examination is necessary and should be comprehensively done to include all the organ system looking for any inborn defects and anomalies. One must focus on the cause of the pain excluding other diseases. The ovarian and uterine mass or enlargements should be looked for by performing the rectoabdominal bimanual examination with much delicacy, however, endometrioma is quite uncommon in adolescents. At times when rectoabdominal bimanual palpation is confusing or the mass is of doubtful character, abdominal or trans labial sonography used [39]. The lesions of endometriosis in adolescents are found commonly in the pouch of Douglas also called the

rectovaginal pouch being the dependent part. Recently, nerve fiber has been studied in an endometrial biopsy gave a promising result for a specificity of about eighty percent and sensitivity of over ninety percent. Biopsied sections of endometrium immunostained with VIP, SP, PGP9.5 and anti-(neuropeptide Y, a calcitonin polypeptide, neurofilament) were all found related to a gene [40]. Thus, a hysteroscope with vaginal approach to biopsy endometrial tissue could be the alternate method of diagnosing in teenagers with endometriosis as a differential diagnosis [41]

4.3 Biomarkers could be the future

Other option for diagnosis could be the biochemical markers that have been studied and researched for several years and their advancements could proof the quickest and noninvasive means of diagnosis. For example, up to now ICAM-1, urocortin, CA-125, follistatin, Ca-19.9, and IL-6 all has shown promising and successful molecules for endometriosis diagnosis [42].

Studies report, CA-125 is a better option for evaluating recurrent cases of endometriosis and in follow-up cases after surgical therapy [43]. Its value was seen increased more often in severe form (III-IV) than in less mild form (I-II) of the disease but does not correlate with the stage of the disease [44]. It may also be found raised in tumors and cancers of the gastrointestinal tract, lung, breast etc. while CA-19.9 could be raised in endometriosis, biliary tract diseases and other benign diseases, but clinically it's mostly used for assessing pancreatic cancers. ICAM-1 was also found raised in endometriosis significantly than in the normal individual without the disease. It was of significant value, especially in deep infiltrative endometriosis(DIE) and peritoneal endometriosis [45] a member of the immunoglobulin superfamily and is involved in the immune and inflammatory response. It has been evaluated as a potential new marker of endometriosis. While among interleukin's family, IL-6 was found raised among individuals harboring endometriosis. It was also found that the combination of biomarkers like ICAM-1 with CA-125 gave the better predictive value especially for DIE [46].

These days a newer group of molecules are being researched and looked for the better biomarker possibilities. For example, urocortin (UCN) along with follistatin (FS) could detect ovarian endometriosis (endometrioma) in comparison with a benign ovarian cyst [47]. In a study, CA-125 showed below fifty percent of ovarian endometriosis with a specificity of just ninety percent while FS showed both sensitivity and specificity above ninety percent [48]

Management

5.1 NSAIDs and OCPs-the first line therapy

Current recommendations by the American College of Obstetrics and Gynecology(ACOG) [62] on the adolescent presenting with a dysmenorrhoea regard initiation of management with NSAIDs and OCPs. Therefore, one must abide by the guidelines and consider NSAIDs and OCPs initially while addressing adolescents with dysmenorrhea [49]. Treatment plan in medicine follows a gradual and stepwise principle. Thus, a chance is taken prescribing NSAIDs to patients with pelvic pain of a non-acute gynecological source, for example endometriosis, dysmenorrhea, and adhesions on the empirical basis. If, possible painkillers should be preserved for the unbearable pain. By decreasing menstrual blood flow and inhibiting ovary, symptomatic patients of dysmenorrhea have also improved with the oral contraceptive beginning with a low dose. Again, it must be stated that one must not only rely on only guidelines and first-line management when employed to deal with teenagers, when special condition arises it may be wise directly proceed with keyhole surgical evaluation rather than wait for three to six months to see an individual in exhausting discomfort that may hamper the academically as well. The individual below sixteen years of age is usually not entertained with GnRH agonist therapy [50]. Empirically in combination with add-back therapy, GnRH therapy is booked for teenagers above eighteen years because of its side-effects on immature bone [50,51].

5.2 Surgical therapy and it's delemma

Since medical therapy is supportive, surgically seems definitive and more rational, and to some extent curative too in terms of pain relief and assuring fertility. Thus, Laparoscopic being minimal invasive it's the best option so far. It is considered the gold standard in diagnosing of endometriosis especially after primary therapy has been exercised. The tool when employed, endometriotic lesions and nodules can be visualized and can aid in a clear diagnosis and at the same time, it can be used for therapeutic use as well [52,53]. However, experts have conflicting opinions when to begin surgical therapy for endometriosis in children. No doubt, whenever surgical treatment to be done laparoscope should be in skilled hand and knowledgeable physician having

a clear idea with various types of lesions in terms of morphology, colour etc. as children have atypical pathology with clearer vesicles and red lesions but fewer standard "powder-burn" lesions [54,55,56,57] and should also be taken as the right concise decision whether or not to resect or ablate the lesions to alleviate the pain. Again, surgical management, all alone is not suitable, especially in adolescence patients because experts believe some residue form of the disease may remain because of which medical management is necessary and believes in avoiding a recurrence of the disease [58] and when a clinical situation demands, repeat laparoscopic surgery can be carried out in a special situation.

When handling pelvic pain, multi-disciplinary tactics, holistic approach, with extended aid for pain management and complementary and alternative therapies, should also be kept in mind while treating adolescents with this disease.

Conclusion

Endometriosis in adolescents is an illness to be reasoned as an important differential diagnosis in pelvic painful sensation and adnexal cysts, particularly among those with pain resistant to the use of commonly used drugs. Endometriosis of adolescence has the likelihood to advance so, when not properly addressed and managed it may further complicate and detroit the health of an individual to the extent from where reversibility is impossible. A true prevention of the consequences of endometriosis is based on the magnified knowingness of the disease in adolescence. Thus, a timely referral to a specialist who is experienced with the laparoscopic diagnosis of endometriosis in adolescents and conservative care may significantly improve their future quality of life.

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