THERAPEUTIC JOURNEY OF ADOLESCENTS AND YOUNG ADULTS WITH SEVERE DYSMENORRHEA AND ENDOMETRIOSIS

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Abstract

Endometriosis, a disorder characterized by the presence of endometrial tissue outside the uterine cavity and commonly accompanied by chronic pelvic pain and infertility, is more common in teenagers and women of reproductive age. Early menarche age, shorter menstrual length, and taller height are connected with a higher risk of endometriosis, while parity, a higher body mass index, and smoking are connected with a infertility or chronic pelvic pain.The medical name for period discomfort or menstrual cramps is dysmenorrhea.

KEY WORDS: Menarche, Infertility, Endometriosis, Dysmenorrhea

Introduction:

The epidemiology of endometriosis and current diagnostic tools and available potential diagnostic biomarkers for endometriosis that may be used to better clinical manage the disease to improve the quality of life of adult and adolescent patient[1] .

The diagnosis of endometriosis is often delayed because symptoms, such as pelvic pain and or infertility, are also associated with other conditions[2,3].Although diagnosis of some types of endometriosis can be accelerated by use of imaging techniques, to date , progress toward validation of a robust noninvasive blood test has been slow [4].Current treatments include surgical removal of lesions and drugs that suppress ovarian hormone production of women undergoing surgery , over half will have a further surgical procedure by five years[5].

Pathogenesis of Endometriotic Lesions:

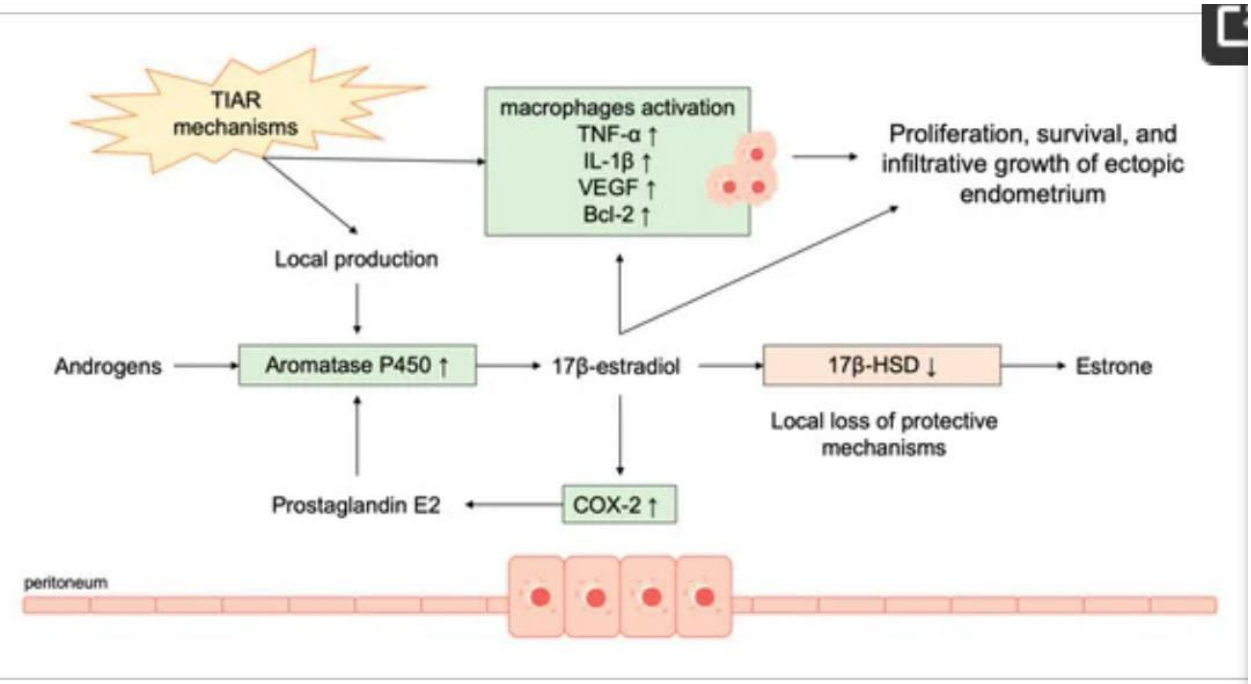
Endometrial tissue-like lesions that develop outside of the uterine cavity are known as endometriosis (EM). The two EM subtypes great degree of similarity may result from pathophysiology[6,7] that has been explored since 1927. Sampson proposed that this occurrence is caused by the presence of retrograde menstruation.Through the tubes, depleted endometrial cells move into the abdominal cavity and stick to the tissue there. This theory is supported by the common sites for EM lesions to manifest, including the peritoneum of the fossa ovaricae, the Douglas region, the sacrouterine ligaments, and the apex vesicae. In anatomical cavities, fluid filled with cells is likely to build up after which the cells "adhere and develop." Although these lesions are frequently superficial, they frequently penetrate the surrounding tissue deeper than 5 mm, a condition known as deep infiltrating endometriosis (DIE).Retrograde menstruation is a well-known occurrence that is frequently observed in women undergoing laparoscopic surgeries, yet about 10-15% of all women experience EM during their reproductive years[8].The immune system, genetic and epigenetic processes, the sort of cells that migrate into the abdominal cavity, as well as environmental and hereditary factors, all play a role[9,10]. The reactivation of the coeloma residuals that are still present in the navel as a result of the physiological omphaloceles accounts for the emergence of primary umbilical EM. They differentiate and finally become EM lesions when hormones are present. Additionally, lesions may form and translocated cells may adhere more readily in the peritoneum itself[11]. Despite the fact that EM lesions are surrounded by an immune response and inflammation, it is very conceivable that an immunological tolerance will develop towards such lesions[12]. The peritoneal fluid of women with EM contains an elevated level of several inflammatory markers [13]. An increase in prostaglandin E2 levels and an elevation of the local aromatase cause a complicated interaction of hormonal and immunological elements to emerge, which primarily result in an increase in estradiol levels. Additionally, the pathogenic environment produced by macrophages drawn to the heme release may encourage not only EM but also precancerous and cancerous tumor’s[14].

Autoimmune illness might develop as a result of persistent immunological factor activation. These are frequent among EM-affected women, although the cause has not yet been

determined[15]. Following the peritoneal fluid's circular flow, peritoneal EM lesions are distributed throughout the abdominal cavity. The right side's paracolic recesses and diaphragm cupola are where lesions are more frequently discovered than the opposite side. Since they almost invariably affect the parts of the intestine that could come into contact with the inner genital organs and seldom impact the colon (ascending/descending) or the transverse colon, DIE, which affects the gut, appears to develop as slap-off lesions [16]. According to G. Leyendecker's "tissue injury and repair theory," the uterus is where the disease first developed. According to this notion, the junction zone (JZ) between the endometrium and the myometrium experiences micro trauma as a result of uterine hyper peristalsis[17,18].Pro-inflammatory mediators are consequently produced, increasing the expression of aromatase. The subsequent locally released estrogen encourages angiogenesis and cell division. As a result, the JZ undergoes alterations that are sonographically represented by an echopoor hem (halo phenomenon), which symbolizes the endometrium's attachment. The border between the endometrium and the myometrium widens in 3D ultrasounds, demonstrating the invasion of endometrial cells into the myometrium[19,20]. Locally produced oxytocin enhances myometrium peristalsis, starting a loop that causes the JZ to be destroyed more and more. Stem cells are presumably triggered during mechanical modification and wound healing processes, and they subsequently emerge from their niche to either cause retrograde menstruation, which results in EM, or to infiltrate the myometrium, which causes AM[21,22].

HIF-1a up regulation is probable in this situation of endometrial-myometrium interface disruption (EMID). The creation of EM lesions and significant immunological alterations are then triggered by HIF-1a, which also activates hypoxia-related molecular biological pathways. It is still unknown whether the alien cells directly alter the immune system or if the immune system is initially defective and unable to destroy the foreign cells. What is known is that in women with EM, both the peritoneum and the peritoneal fluid exhibit significant inflammatory reactions and several immunological alterations[23].The development of the accompanying lesions is highly correlated with these immunological results, and chronic inflammation is becoming a more important component of pathophysiological theories. Notably, ectopic EM lesions contain smooth muscle cells in addition to epithelial and stromal cells, regardless of where they are found (peritoneal lesion, endometrium at the ovaries, DIE, or in extra genital manifestation in the navel, the abdominal wall, or in the groyne). They all have estrogen and progesterone receptors, as well as oxytocin and vasopressin receptors. As a result, these lesions are tiny uteri as well as settlements that resemble endometrial tissue. The differentiation of smooth muscle cells varies, and the process of muscular metaplasia emphasizes the formation of lesions from pluripotent cells[24] Mesenchyme stem cell-like cells have been found to exist in menstrual blood. These have the capacity to differentiate into mesodermal, endodermal, and ectodermal cells, which explains why ectopic "miniature uteri" exist[25]. Another intriguing detail regarding the complexity of the disease's origin is revealed by the description of EM cases in males[26]. The myofibroblast transformation (FMT), involving fibroblasts and collagen I release, enables the

lesions to take on new forms [27]. Endometriosis lesions are always accompanied by fibrotic alterations in the surrounding tissue.



Epidemiology and risk factors

Hormonal variation may significantly affect the risk of developing endometriosis, according to a number of reproductive parameters that have been consistently linked to endometriosis risk. For instance, a young age at menarche [28,29] and a short menstrual cycle length(Moen MH,Schei B.Epidemiology of endometriosis in a Norwegian country)are linked to a higher risk, whereas parity and the use of an oral contraceptive[30,31] now are linked to a lower risk. Women at an earlier age at menarche and those who are nulliparous have higher levels of the hormones circulating estradiol and estrone, which encourage ectopic and eutopic endometrial tissue[32,33]. Body mass index (BMI) and endometriosis have a persistent negative relationship, despite neither being reproductive risk factors; this relationship may be related to hormonal variations between obese and thin women[28,29].

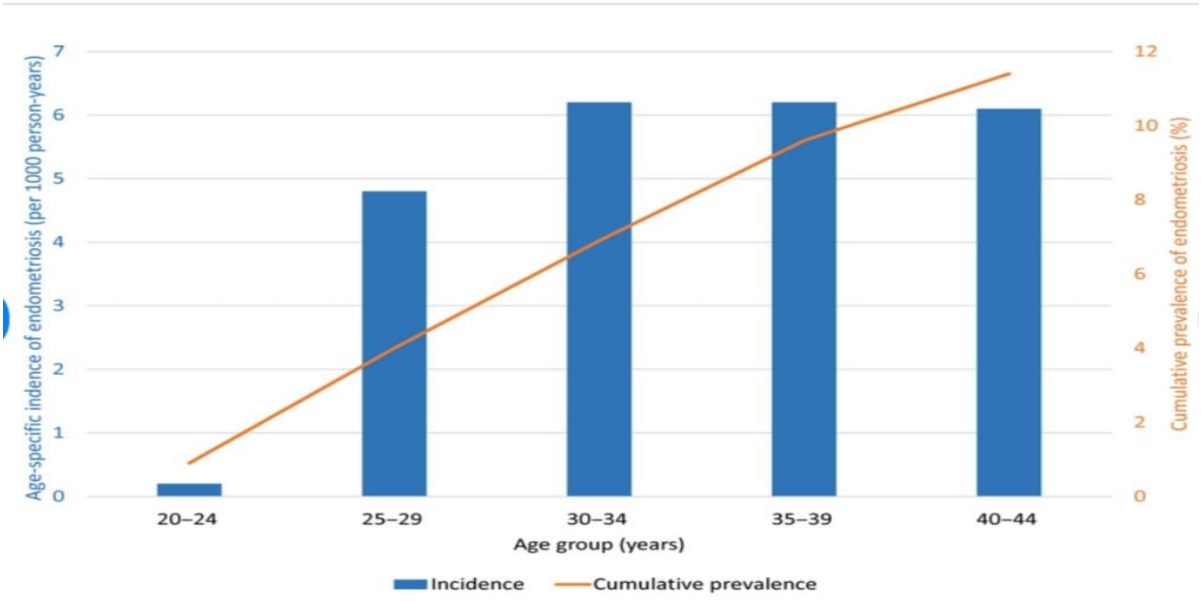
Consequently, methodological problems have hindered the assessment of tubal ligation, parity, and oral contraceptive use in connection to endometriosis risk. It has been proposed that tubal ligation reduces the risk of endometriosis by preventing retrograde menstruation from entering the pelvic cavity. However, since endometriosis is defined by infertility and women who seek a tubal ligation are more likely to be parous than the general population, the correlation between tubal ligation and endometriosis is difficult to evaluate[34,35]. The risk of endometriosis is inversely correlated with oral contraceptive use, with most studies [36] though not all, showing a decreased risk for current users but an increased risk for former users. However, since endometriosis-related pain is managed with oral contraceptives, this relationship may indicate

that endometriosis symptoms have been suppressed while on oral contraceptives that reappear after the oral contraceptives are stopped.

It's unknown whether smoking causes endometriosis. Smoking, though harmful to many other aspects of health, has been linked in some studies—but not all—[37,38]to a lower incidence of endometriosis. It's interesting to note that while passive smoking exposure during infancy increases risk, exposure to cigarette smoke during pregnancy is related with an 80% reduction in endometriosis risk[39]. Circulating oestrogen levels are known to be lower in women who smoke, which may be able to prevent the formation and persistence of endometriotic tissue, even though the exact mechanism is unknown.

The relationship between drinking alcohol and caffeine has contradictory results and may be dependent on one's reproductive status. Numerous studies have found that drinking more alcohol or caffeine[40] increases risk in infertile women. The link is biologically supported by higher levels of bioavailable oestrogen in women who drink in moderation. However, research that is not limited to infertile women has found no correlation[41].

Other dietary habits and lifestyle choices that affect endometriosis risk can be related to how well they can reduce inflammation. Interleukin 6 (IL6), TNF-alpha, and other inflammatory markers may be decreased by physical activity and omega-3 dietary fatty acids[42] . Higher intake of long-chain omega-3 fatty acids has been linked to lowered endometriosis risk[43], while the relationship between exercise and endometriosis is uncertain.



GRAPH -1 Adolescents are more effected to endometriosis than young adults due to delayed diagnosis. [44]

Endometriosis: subtypes, symptoms, and classification as a ‘‘disease’’

Types of endometriosis and their diagnosis:

1.**Superficial peritoneal endometriosis**: which makes up around 80% of cases, ovarian (cysts or "endometriomas")

2. **Deep endometriosis**: are the three kinds of endometriosis that occur in the pelvic cavity [2,3].

Endometriosis lesions have also been discovered in extra-pelvic locations, such as the central and peripheral nervous systems, upper abdominal visceral organs, abdominal wall, diaphragm, and pleura [45].

Symptoms and reclassification as a ‘‘syndrome’’

Chronic pelvic discomfort (cyclical and noncyclical), painful periods, unpleasant sex, and pain during urination and defecation are all frequent signs of endometriosis (Figure 1). Women with endometriosis report experiencing exhaustion and depression, which are symptoms shared by people with other chronic pain illnesses. Patients with endometriosis experience sub/infertility at considerably higher rates than the general male population. When compared to disease stage according to the ASRM criteria, there are consistently poor relationships between the quantity/location/type of lesions and the symptoms of pain reported by the patient [46].

There is disagreement over whether superficial peritoneal endometriosis can develop into another subtype or regress on its own in terms of the disease's natural history. It is even less clear what causes extra-pelvic endometriosis. These concerns have given rise to the hypothesis that if we stop thinking of endometriosis as a singular "disease" with a diagnosis based purely on the existence of lesion(s) resembling endometrium, we may make more progress in creating patient-focused treatments. The illness model, in our opinion and that of others, is flawed, not only because to the poor association between the quantity/location of lesions and pain sensations, but also due to Figure 1. Numerous symptoms are linked to endometriosis. Symptoms related with the disorder that are most frequently reported include pain, bowel, and bladder symptoms as well as those that are shared by other chronic pain conditions, like exhaustion and depression. Because they overlap with several other conditions, the ranges of symptoms (which may or may not appear in all patients)add to the acknowledged delay in diagnosis. as much to 50% of asymptomatic fertile women seeking other surgical procedures may have lesions, according to estimates [47].

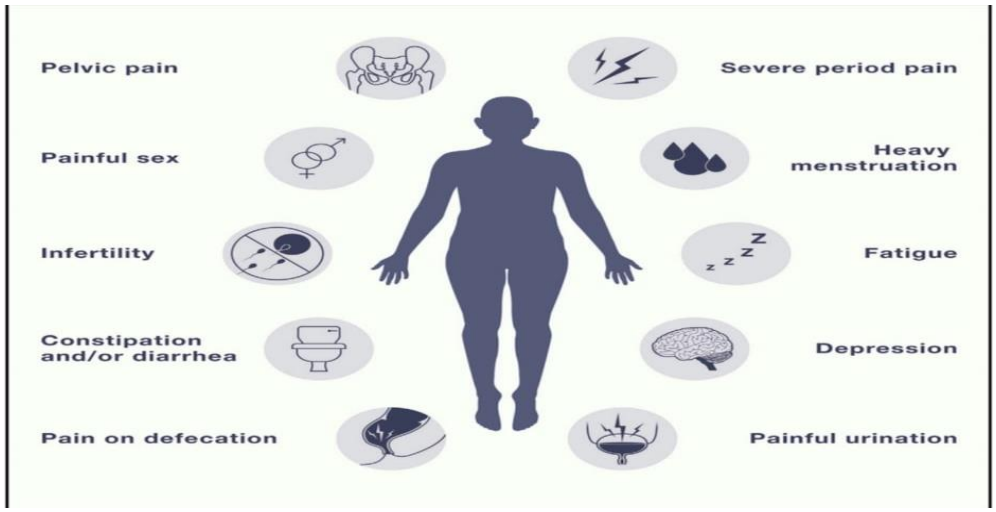


Figure 1. Endometriosis is associated with a wide range of symptoms Summary of the most common symptoms associated with the condition, including pain, bowel, and bladder symptoms, as well as those that are also associated with other chronic pain conditions, such as fatigue and depression. The ranges of symptoms (that may or may not occur in all patients) contribute to the recognized delay in diagnosis because they overlap with these other conditions [48].

DIAGNOSIS

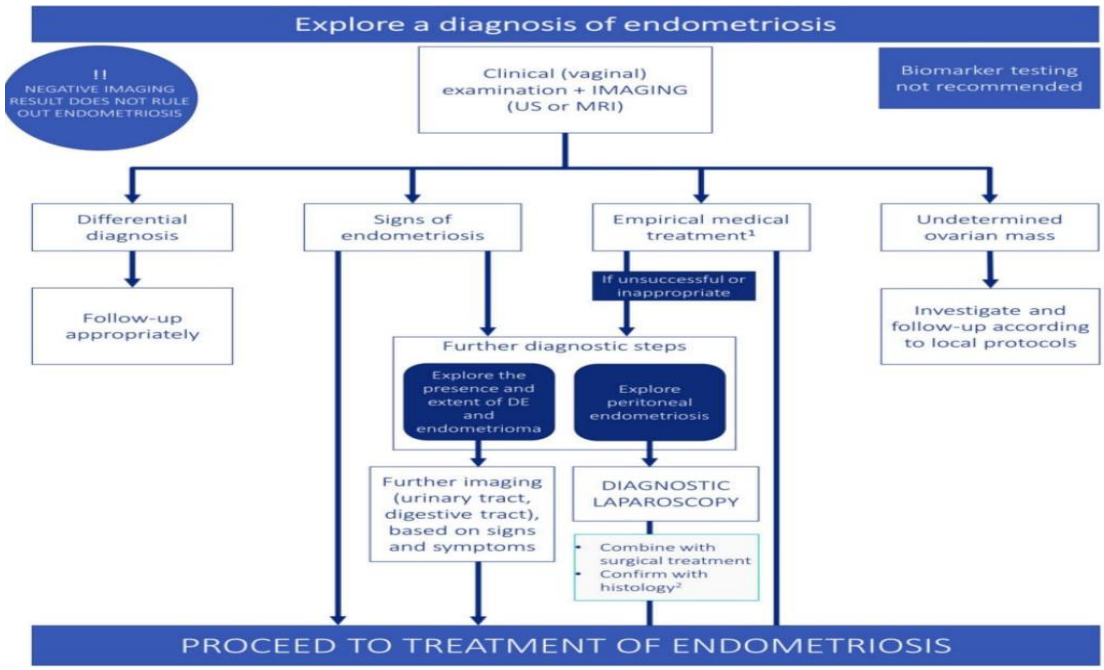


Figure 2. **The recommended diagnostic process for endometriosis**.DE, deep endometriosis; US, ultrasound. attempts should be made to relieve symptoms, either by empirical treatment or after a diagnosis of endometriosis (conclusion, not recommendation)[49].

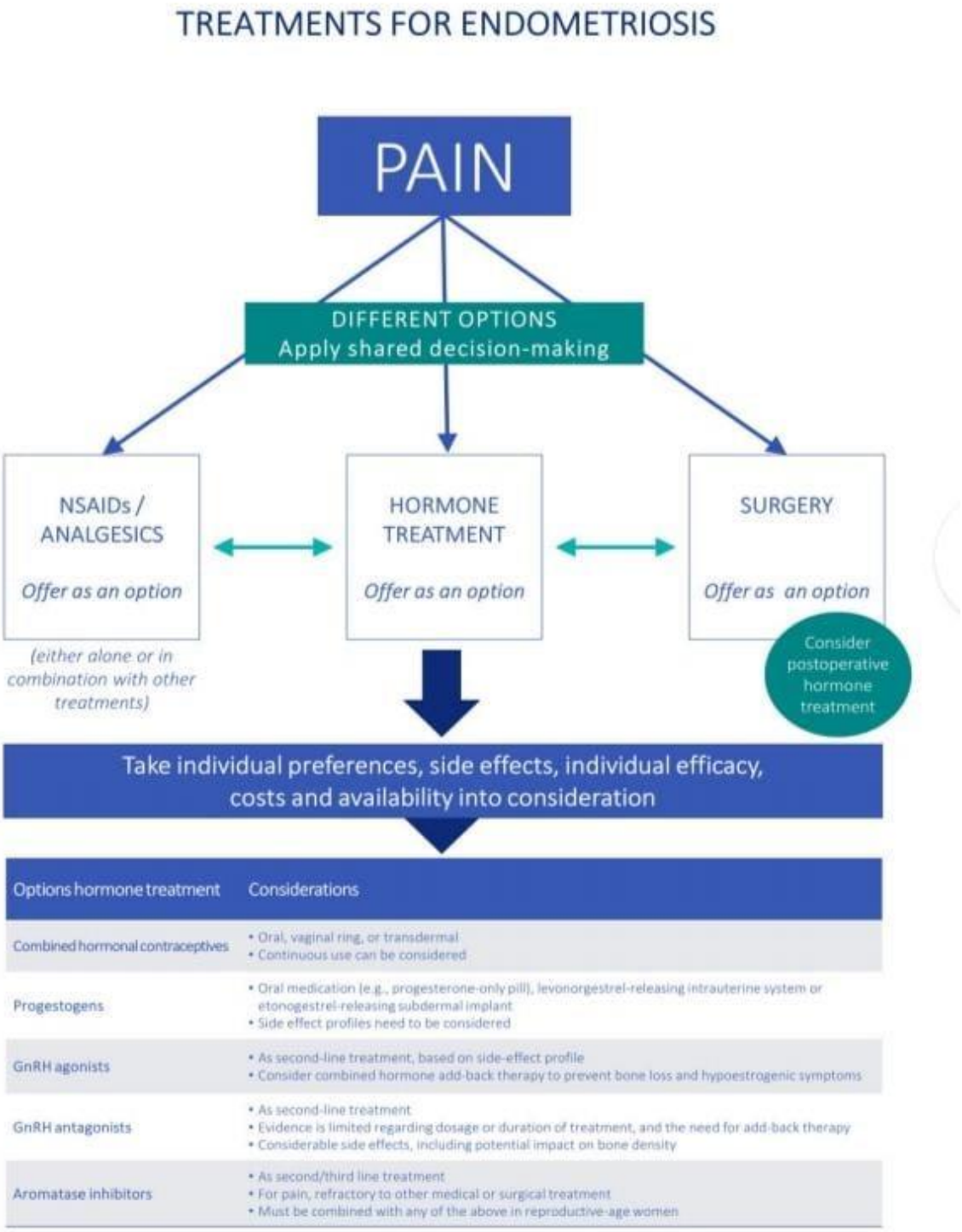


Figure: 3 ***Summary of the recommendations for treatment of pain symptoms linked to endometriosis.*** *NSAID, non-steroidal antiinflammatory*[50].Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis associated pain and improves quality of life.[51].

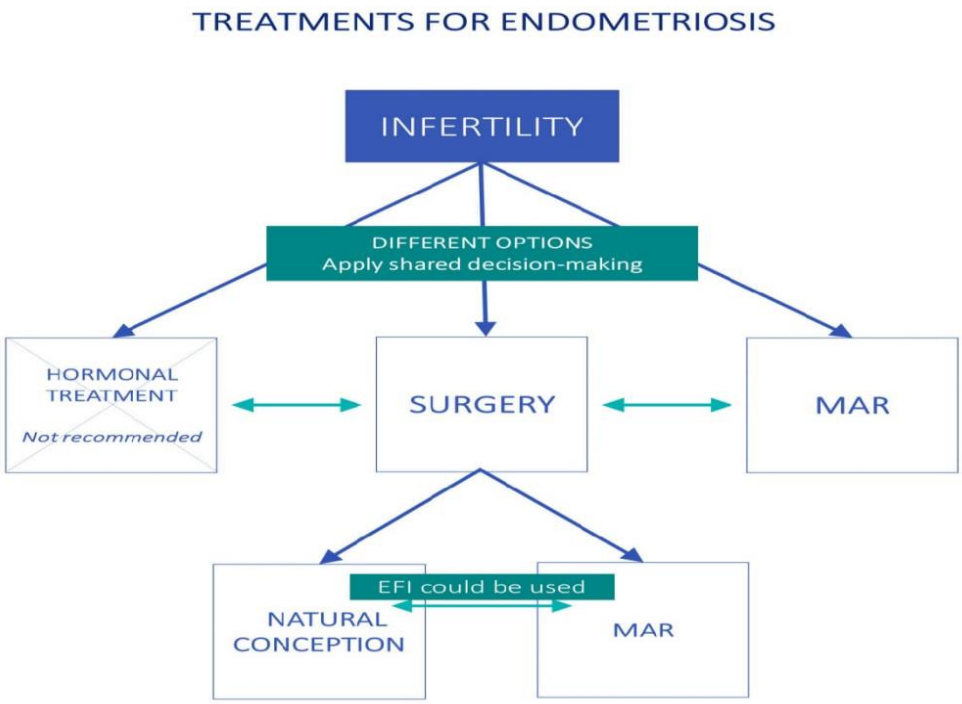


Figure 4. Summary of the recommendations on treatment of endometriosis-associated infertility. EFI**, (**endometriosis fertility index)**;** MAR,(medically assisted reproduction)[50].

Are hormone/medical therapies effective for treatment of endometriosis-associated infertility?

In infertile women with endometriosis,clinicians should not prescribe ovarian suppression treatment to improve fertility[52].

Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates[53].

Those women who cannot attempt to or decide not to conceive immediately after surgery may be offered hormone therapy as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain[53].

Drug	Mode of administration	Mechanism of action	Recommended length of treatment	Side effects
Combined oral contraceptives	oral (can be taken continuously), patch, or ring	ovarian suppression[a]	long term	nausea, headaches
Progestogens	oral or intramuscular depot injection or intrauterine system or subdermal implant	endometrial regression, some ovarian suppression[b]	long term	weight gain, bloating, acne, unscheduled bleeding (amenorrhea common after prolonged depot use)
Antiprogestogens	oral	ovarian suppression[a]	long term	unscheduled bleeding, estrogen deficiency, masculinization
Gonadotrophin-releasing hormone agonists	subcutaneous or intramuscular injection	ovarian suppression[a]	6 months	vasomotor symptoms, vaginal dryness, sleep disturbance
Gonadotrophin-releasing hormone antagonists	oral	ovarian suppression[a]	6 months	vasomotor symptoms, vaginal dryness, sleep disturbance
Aromatase inhibitors	oral	reduction in aromatase activity in endometriosis lesions	6 months	vasomotor symptoms, decreased libido

Table-1 Hormone suppressive drugs used in the treatment of endometriosis[48].

Conclusion

In conclusion, endometriosis is a debilitating condition that affects both adult and adolescent patients' quality of life. Diagnostic delays are frequent and can affect fertility and reproductive potential. To detect patients early in the illness process and improve outcomes, including reduced discomfort and better fertility, a semi- or non-invasive diagnostic biomarker would be valuable. Endometriosis has been linked to a wide range of biomarkers, however none of them are sensitive or specific enough to be used in screening. By early detecting the instances, these possible biomarkers could lower the cost of surgical intervention and enhance clinical disease care. Consequently, additional study in this field of medicine is required.

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