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ENDOMETRIOSIS WITH INFERTILITY

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Abstrct: Endometriosis represents a frequently diagnosed gynaecological affliction in the reproductive timespan of women, defined by symptoms ranging from pelvic pain to infertility. A complex interplay between the genetic profile, hormonal activity, menstrual cyclicity, inflammation status, and immunological factors define the phenotypic presentation of endometriosis. To date, imaging techniques represent the gold standard in diagnosing endometriosis, of which transvaginal ultrasonography and magnetic resonance imaging bring the most value to the diagnostic step. Current medical treatment options for endometriosis-associated infertility focus on either stimulating the follicular development and ovulation or on inhibiting the growth and development of endometriotic lesions. Techniques of assisted reproduction consisting of superovulation with in vitro fertilization or intrauterine insemination represent effective treatment alternatives that improve fertility in patients suffering from endometriosis. Emerging therapies such as the usage of antioxidant molecules and stem cells still need future research to prove the therapeutic efficacy in this pathology.

Keywords: endometriosis, infertility, etiopathogenesis, treatment.

INTRODUCTION

Endometriosis is a challenging condition of reproductive-aged women, causing problems ranging from chronic pain to infertility. It is characterized by an oestrogen-dependent stroma and endometrial glands found predominantly, but not exclusively, in the pelvic compartment [1]. Due to the necessity of surgical visualization for a definite and clear diagnostic, a precise evaluation of the prevalence and incidence of the disease is hard to obtain [2]. This disease is characterized by a prevalence estimated at 5%, peaking between 25 and 35 years [3], and an annual incidence among women aged 15–49 years, evaluated at 0.1% [4], generating thus significant healthcare costs (according to a study conducted by Simoens et al., the average annual cost per woman was estimated at €9579 [5]).

Although the relation between endometriosis and infertility as a matter of a definitive cause-effect connection is still debatable, it is clinically recognized and well supported throughout the literature [6]. Currently, endometriosis-associated infertility is viewed as a multifactorial problem, facing matters related to altered immunity and genetics, that affects not only the fallopian tubes and the embryo transport but also the normal endometrium [7]. To date, treating infertility caused by endometriosis is focused on removing or reducing ectopic endometrial implants and restoring the normal pelvic anatomy either by medical, surgical, or assisted reproductive technologic means [8]. The medical approach targets the ovarian function, blocking it with various drugs such as agonists of gonadotropin-releasing hormone and oral contraceptives [9].

Assisted reproductive technologies (ART), such as in-vitro fertilization (IVF) come into play when neither medical nor surgical attempts meet the required outcome [10]. IVF has been demonstrated to represent one of the key treatment options for patients suffering from endometriosis-associated infertility, especially when it involves a compromised tubal function, aberrant peritoneal anatomy, or failure of other treatment methods [11].

This manuscript constitutes a critical review and analysis of the literature and focuses on the epidemiological and clinical aspects of endometriosis as a disease and the current tools used for diagnosing this ailment, as well as several proposed mechanisms for infertility development and its current treatment options.

Materials and methods

Risk Factors for Developing Endometriosis

Even though significant insight was gained on the disease through research initiatives in the last decades, the exact cause of endometriosis remains unclear. It has been accepted that the genetic profile, hormonal activity, inflammation status, and immunological environment, play an important role in the manifestation and progression of endometriosis [12]. From an epidemiological perspective, it is regarded currently that an intertwined relationship between socio-economic status, family history, constitutional factors, personal habits, reproductive and gynaecological status, as well as environmental factors, constitutes one of the first steps regarding the occurrence of endometriosis [2,13].

Concerning the environmental factors, it has been suggested that exposure to elevated levels of polychlorinated biphenyls [14], dioxin [15], phthalate esters, bisphenol A [16] or organochlorinated pollutants and perfluorochemicals may play a role in the development of endometriosis. Some theories regarding the mechanism of action by which these pollutants are involved in initiating the disease include generating oxidative stress which can modulate the immunological activity or alter the hormonal homeostasis, however, further research is needed to shed light on the exact pathways of the intervention of these toxins regarding endometriosis [13].

As for behavioural traits, the relationship between dietary preferences, alcohol and caffeine intake, smoking, and physical activity in regards to involvement in developing endometriosis has been studied [17]. Some dietary preferences, generally related to consumption of red meat, have been associated with higher incidence related to developing endometriosis, while others, such as consumption of fresh fruits and vegetables, have shown to diminish this risk [18]. It has been hypothesized that caffeine and alcohol intake might play a role in endometriosis pathogenesis by altering reproductive hormones via aromatase activation which increases the conversion of testosterone to oestrogen [19,20]. While it is well known that smoking increases the inflammatory status and alters the hormonal balance, one meta-analysis concluded that there is little evidence to link tobacco smoking to endometriosis, even in the case of heavy users. Taking into account the risk of physical activity on endometriosis, it has been hypothesized that intense physical activities might stimulate endometrial proliferation by increasing oestrogen levels and insulin-like growth factor-1 , while normal intensity exercise might have a protective effect by reducing the inflammatory status and oxidative stress .In terms of reproductive and gynaecological factors, most of the risk factors associated with endometriosis focus on age at menarche, menstrual cycle length, duration of flow, and parity . Menarche starting at an early age and long and heavy menstrual cycles have been correlated with higher risk due to higher concentrations of oestradiol and estrone, while parity and oral contraceptive usage [were related to protective status. Even though tubal ligation has been thought to decrease the risk of the disease by inhibiting endometrial cells to reach the pelvic compartment , patients receiving this treatment might represent a biased group of asymptomatic patients with fewer gynaecologic and reproductive problems than women seeking nonsurgical methods of contraception, making the association difficult to interpret [18].

Clinical Features of Endometriosis

The clinical presentation of reproductive-aged women suffering from endometriosis is highly variable, with symptoms ranging from pelvic pain, dysmenorrhea, to infertility, thus having a serious impact on the mental and socioemotional well-being of the patient [1]. Pelvic pain is characterized by a dull, sharp, throbbing, or burning sensation, while dysmenorrhea is described as pelvic pain that presents before, during, and/or after menstruation. Compression and infiltration of the nerves in the endometrial lesions represent the main cause of pain development in endometriosis, although other mechanisms such as the nociceptive pain component of neuropathic pain, neurogenic inflammatory processes, and myogenic pain along with alterations in peripheral and central nervous system pain processing have been considered in generating the endometriosis-associated pelvic pain complex pathology.

Diagnostic Tools for Endometriosis

Diagnosing endometriosis requires a vast array of tools related not only to clinical assessment but also to biological clues as well as imaging techniques, whether non-invasive such as ultrasonography or surgical methods for direct visualization. Evaluating the presence of symptoms and performing a physical examination represent the first steps in diagnosing endometriosis. As mentioned, before, symptoms of endometriosis correlate with the site of anatomical involvement, thus, women are complaining most frequently of cyclic pelvic pain in the form of dysmenorrhea, intermenstrual pain, and dyspareunia.

Physical examination, while executing the bimanual pelvic manoeuvre, points toward diagnosing endometriosis when several criteria are met such as palpable nodularity and abnormal pelvic anatomy, especially when located in the vagina and the rectovaginal space, the pouch of Douglas, the rectosigmoid, as well as the posterior wall of the urinary bladder [. Other signs such as tenderness, decreased mobility, and a retroverted uterus, evidenced while palpating, might also indicate signs of endometriosis. During speculum inspection, endometriosis might be present in form of red or blue hypertrophic and haemorrhagic nodules, usually in the posterior fornix. Nevertheless, a normal clinical examination does not eliminate the diagnosis of endometriosis, further investigations such as laboratory and imaging techniques being required to assess the extent and impact of the disease.

Imaging techniques have an important role in aiding the endometriosis diagnostic, whether non-invasive or invasive in nature, due to their power of pointing the exact location of lesions and assessing the disease extent. In this regard, numerous non-invasive imaging tools can be used, including ultrasonography and magnetic resonance imaging.

Ultrasonography represents one of the cheapest, highly available, and non-invasive imaging tools for assessing endometriosis, either by transabdominal, transvaginal, or transrectal approach, being frequently used as an incipient screening test for endometriosis, as well as a preoperative tool for estimating the length of the surgical manoeuvres. This imaging technique is most used in evaluating the endometriotic cysts that usually present a varied sonographic spectrum ranging from anechoic cysts, cysts with diffuse low-level echoes to solid-appearing masses, that occasionally present septations, thickened walls, and wall nodularity, with pericystic blood flow. Due to the high variation in sonographic characteristics, endometriosis lesions might be similar in appearance with other ailments such as dermoid cysts, haemorrhagic cysts, neoplasms, ovarian abscesses, and ectopic pregnancies, thus thorough differential diagnosis is needed to exclude the possibility of misdiagnosis.

To date, transvaginal ultrasonography represents the standard imaging technique for identifying ovarian endometriomas due to its high values in sensitivity (93%) and specificity (97%) when performed by an expert operator vertheless, transvaginal imaging has lower success rates in the visualization of adhesions or superficial peritoneal implants, thus a transabdominal approach or the use of magnetic resonance imaging can be more useful. Transrectal ultrasound has been also useful in aiding the endometriosis diagnostic,

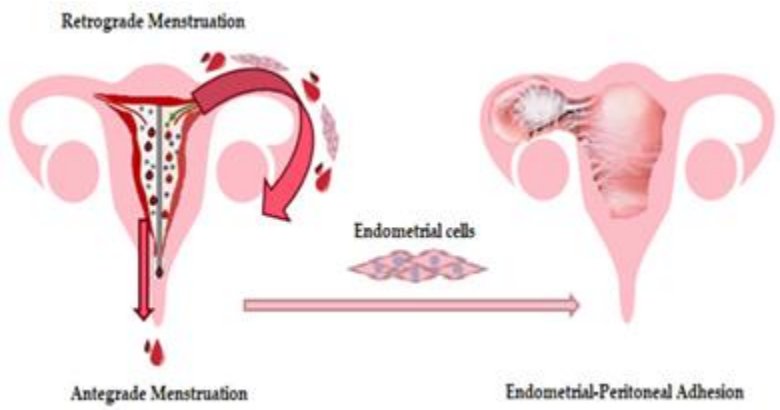
especially when assessing the extent of infiltration of the rectal and the posterior bladder walls .Numerous attempts have been made to standardize the ultrasonographic method in order assure a complete evaluation of the lesions and in 2016, an international consensus group implemented a four-step systematic approach which includes four steps, respectively: in the first step a routine evaluation of uterus and adnexa is conducted, focusing on ultrasonographic features of adenomyosis and endometrioma; in the second step tenderness and ovarian mobility is evaluated; the third step involves assessment of the pouch of Douglas using the 'sliding sign'; the fourth step focuses on exploring the anterior and posterior compartment, assessing deep infiltrative endometriosis nodules . Despite all efforts, the main challenge of imaging endometriosis remains the detection of deep infiltrative lesions into the pelvic structures as well as non-ovarian cases, for which MRI evaluation is better suited

Extensive efforts have been conducted to standardize the systems scores used to grade the disease's extension by a consensus group focused on reproductive medicine that have materialized in the form of a classification system. This system assigns corresponding values to endometriotic lesions regarding the size of the lesions and the presence of adhesions material found on the gynaecological structures. It is compartmentalized into four stages pertaining to the severity. Despite its high sensitivity and specificity scores in detecting endometriosis, MRI presents some limitations in regard to its performance, mainly in cases of intestinal deep infiltrating endometriosis by reduced bowel peristalsis, in cases of anatomical variations of structures such as the rectovaginal septum or in the situation of a retroflexed uterus. Such events may impair the accuracy of diagnostics, thus calling for a surgical approach in aiding the assessment of the disease extent.

Mechanisms Involved in the Pathogenesis of Endometriosis-Associated Infertility

Understanding the intricate mechanisms concerning the etiopathogenesis of endometriosis and infertility as a complication, was an enigmatic task in the era of limited diagnostic techniques, when the genetic, cytogenetic, and molecular tools were not yet fully developed. Although several studies have been focusing on the topic, there still little agreement regarding all the aspects that link these two medical entities. To date, in the case of not objectifying anatomical distortions such as adhesions and fibrotic tissue, few mechanisms shed light on the exact steps that lead to infertility. Over the years, the most acknowledged theory concerning the etiopathogenesis of endometriosis was that of the retrograde menstruation, described by the endometrial cell implantation in different peritoneal locations, cells that sidestep the fallopian tubes and implant in the peritoneum, where the newly created immune microenvironment aids in the survival of these cells (Figure 1) .

Figure 1.



As the theory of retrograde menstruation stipulates, the implantation of viable endometrial cells in the peritoneal cavity is facilitated by the constant reflux of endometrial debris during menstruation, leading to an inflammatory microenvironment in this anatomical compartment.

While endometriosis is a chronic inflammatory disease that involves the presence of extrauterine endometrial-like tissue, adenomyosis is a benign condition that occurs at the level of uterus, within the myometrium, being characterized by the presence of ectopic endometrial tissue glands and stroma in this area. This particular condition is usually diagnosed while investigating with other gynaecological comorbidities such uterine fibroids and endometriosis. Several hypotheses have been proposed, but a common definition of adenomyosis remains controversial due to theories regarding the pathogenesis, diagnostic criteria, and classifications of this disease.

Although adenomyosis has many features in common with endometriosis and often coexists, they are considered two different pathologic entities. Following numerous studies on these two gynaecological diseases so similar that adenomyosis was called internal endometriosis, many differences in clinical manifestations, risk factors, and pathogenesis were discovered. However, there are many similarities between the two conditions in terms of molecular aberrations, hormonal and immune system disorders, and clinical manifestations.

Regarding female fertility, it has been suggested that 30–50% of those diagnosed with endometriosis are infertile], with an increase of up to 80% in such patients following assisted reproduction techniques (ARTs) Although adenomyosis has been considered a typical uterine condition identified in multiparous women over the age of 40, recent studies and modern diagnostic imaging methods have demonstrated the presence of this disease in young women as well. Regarding the association with infertility and reproductive failure the evidence suggests that the percentage of adenomyosis prevalence is variable between 20% and 40% in cases of recurrent pregnancy loss, and about 35% was reported in previous ART failure.

Functional and structural changes in the eutopic endometrium and inner myometrium are characteristic of endometriosis and adenomyosis, these changes having negative consequences for female fertility. Altered endometrial receptivity in patients with endometriosis and adenomyosis is also linked to some molecular events that are associated with the process of implantation and embryo development.

Disorder of these processes is associated with an increased likelihood of abnormal endometrial molecular expressions of genes that are part of the homeobox (Hox) gene family, as well as other autocrine and paracrine factors, growth and transcription factors, steroid hormones, molecules cell adhesion, immune and inflammatory mediators, and other factors, including myometrial contractility and uterine peristalsis.

Along with the technological advancements, several new mechanisms that could explain this link have been proposed such as endocrine and immunological abnormalities. From an endocrine perspective, most of the theories take into consideration defects in folliculogenesis and ovulation, as well as abnormal hormonal serum levels such as hyperprolactinemia. Mechanisms concerning the immunological alterations focus on events like sperm phagocytosis, embryotoxicity along with implantation defects that happen due to alteration on a molecular level. Nevertheless, several factors complicate the advancements of this research domain due to matters related to the disease such as the phenotypic heterogeneity and the higher under diagnostic rates compared to other diseases as well as management issues due to the lack of thorough indexing and registering on a national and international scale.

Biochemical and Immunological Traits that Associate Infertility to Endometriosis

The link between infertility and endometriosis is complex, and understanding it implies unravelling multiple intricate pathways. From a biochemical perspective, oxidative stress represents one of the most researched factors linked to endometrial induced infertility. Aberrant increased levels of reactive oxygen species (ROS)

resulted from oxygen metabolism impact the endometrial cells by damaging not only proteins and lipids but also DNA structure, thus altering the cellular cycle and function. One study focused on assessing the biochemical imbalances for women undergoing surgery for gynaecological problems, found increased serum levels of such markers including advanced oxidation protein products as well as nitrates/nitrites, especially in patients suffering from advanced stages of endometrial disease.

Medical Treatment Options

Medical therapy for patients with endometriosis-associated infertility involves two strategies, with the main purpose of improving fertility: either stimulation of ovulation and of the follicular development process or suppression of follicular development to generate amenorrhea and inhibit the enlargement of endometriotic lesions. A Cochrane review showed that suppressing ovulation using gonadotropin-releasing hormone (GnRH) agonists, oral contraceptives, progestins, and danazol is not considered a suitable therapeutic option for women suffering from infertility associated with endometriosis due to similar outcome regarding pregnancy when compared with women on placebo or no treatment.

Medical treatment with these therapeutic agents tends to ameliorate pain symptoms, but they usually cause subfertility and therefore are not useful for patients with endometriosis-associated infertility with the purpose of increasing pregnancy rates and live births.

For ovulation induction, clomiphene citrate has been the most widely prescribed treatment, either alone or combined with gonadotropins. Another medical treatment for endometriosis includes aromatase inhibitors, that also stimulate the ovary, but they cause functional ovarian cysts, so in premenopausal women, they should be administered in combination with GnRH agonist, progestins, or combined oral contraceptive.

For younger infertile women (under 35 years) with minimal-mild endometriosis, a good first-line treatment is represented by expectant management or the use of superovulation (SO) with intrauterine insemination (IUI). Older women with stage I–II endometriosis-associated infertility can greatly benefit from be a more aggressive treatment with SO/IUI or IVF. For infertile patients suffering from stage III–IV endometriosis, conservative surgery with laparoscopy or possible laparotomy could be the best available therapeutic option. IVF may be an efficient treatment for women with moderate to severe endometriosis, if all the aforementioned treatments do not meet the desirable fertility outcome.

It was proven that prolonged treatment with GnRH agonists before IVF or ICSI may improve pregnancy outcomes in women suffering from advanced forms of endometriosis. Pre-treatment with GnRH agonists can improve the oocyte quality and the ovarian microenvironment.

Surgical Treatment Alternatives

Surgical treatment options in endometriosis-associated infertility are laparotomy, laparoscopy, or robotic surgery. Laparoscopic intervention is most frequently used due to its advantages, including a lower cost and a shorter recovery and hospitalization [7]. Surgical intervention aims to remove endometriotic implants and endometriomas and restore the normal pelvic anatomy to the greatest possible extent. Literature data have shown that laparoscopy surgery in minimal-mild endometriosis improves fertility and live birth rates. In moderate-severe endometriosis, the laparoscopic surgery can treat pelvic adhesions, but unfortunately, there are insufficient randomized controlled trials on postoperative pregnancy rate.

Newer studies suggest that laparoscopic surgery as an investigative and corrective tool of the underlying pathologies prior to initiating numerous and various therapeutic attempts, should be taken into consideration for women suffering from unidentified infertility aetiology, as it can greatly impact the outcome, as well as improving the overall costs of the lengthy treatment plan and ultimately the quality of life of the women going through this journey towards child conceiving. The same view on laparoscopic investigation prior to

concentrating on assisted reproduction techniques is shared when focusing on mild male factor infertility cases, especially if previous failed IVF have attempts attributed to an infertility aetiology.

The most common in vivo technique is intrauterine insemination (IUI) that includes follicle stimulation or not, followed by the transfer of the semen into the uterine cavity. The most frequently in vitro method used in couples with a standard sperm count is in vitro fertilization (IVF). In situations of severely decreased sperm quality, an intracytoplasmic sperm injection can be used as a therapeutic option to increase rates of a good fertility outcome (ICSI).

Patients with minimal to mild endometriosis that have been surgically diagnosed and have not shown any anatomic distortion, were directed to ovarian stimulation (with gonadotropins or clomiphene citrate) followed by IUI, which can be a suitable alternative to IUI alone or IVF.

Systematic reviews reported that second-line conservative surgery for recurrent endometriosis has a negative effect on the IVF outcomes. The number of mature oocytes retrieved following IVF procedure and high-quality embryos was considerably reduced after second-line conservative surgery than after the initial conservative surgical intervention. Second-line surgery seems to significantly diminish the ovarian reserve and therefore this procedure should be attentively considered as an alternative therapeutic method of women who desire a future pregnancy.

CONCLUSION

Endometriosis is a disorder that affects women of reproductive age, causing pain and infertility problems. Even though the association between infertility and endometriosis is still controversial, it is clinically recognized and well supported by many studies.

The treatment of endometriosis-associated infertility consists of reducing or removing the ectopic endometrial implant and restoring normal pelvic anatomy through medical and/or surgical treatment and assisted reproduction technology. Medical treatments of endometriosis-associated infertility tend to ameliorate pain symptoms, but they are not effective in infertility treatment. These treatments should be utilized as an adjuvant to ART.

ART includes IUI and IVF and comes into play when neither medical nor surgical therapy meets the desired outcome. IUI is efficient in patients with minimal to mild endometriosis, that have been surgically diagnosed and have not shown any anatomic distortion. IVF has shown to be the most successful treatment for infertile women with severe endometriosis.

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