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Research Article

Underlying Anomalies that May Contribute to decreased Fertility in Patients with Endometriosis

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Abstract

Endometriosis is a chronic, estrogen dependent, progesterone resistant and inflammatory disease that affects up to 10% of general population, but the incidence rises to 50%, when patients address for infertility. The objective of this review is to highlight the underlying mechanisms that can be responsible or further negatively influence fertility in patients diagnosed with endometriosis. Aside from the challenges regarding the qualitative assessment of the reproductive status of patients, fertility in endometriosis is additionally decreased by peculiar underlying mechanisms, which contribute to the pathophysiology of infertility. Among them, we would like to mention the inflammatory syndrome, which induces anomalies of peritoneal fluid and local environment, pelvic anatomy, ovaries, uterine cavity, and associates profound alterations often difficult to diagnose. The inflammatory syndrome related to endometriosis may be partially responsible for the sub or infertility that associates the condition. In addition, the adherences and pain syndrome that accompanies endometriosis and the impaired sexual function deepen the preexisting fertility anomalies. One other aspect, often unheeded, is the concurrent adenomyosis, which shares biological and molecular features with endometriosis, and is believed to complicate even more both fertility and pregnancy's outcome. In conclusion, assessing mechanisms and processes that could decrease fertility, as well as emphasizing the correlation established between them, is of great importance in the management of endometriosis induced infertility and patient's quality of life.

Keywords: Adenomyosis; Adherences; Antimullerian Hormone; Endometriosis; Fertility; Inflammation; Pelvic Pain; Sexual Function

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Introduction

Endometriosis is a chronic, estrogen dependent, progesterone resistant, inflammatory and challenging disease, and is diagnosed in up to 10% of women, and up to 50% of women addressing for infertility [1]. The complex medical condition affects the reproductive age patients and its consequences extend beyond medical symptoms and signs, and relate to decreased fertility and quality of life [2]. Of unknown origin, the disease has been under close attention among medical personnel, and studies have been performed in order to better clinically assess, classify, understand the pathogenesis and develop a standardized treatment protocol. Aside from the unspecific and various clinical symptoms, that often delay the diagnosis, patients seek medical care when fertility is involved [3]. Reproductive status rises greater concerns when endometriosis in diagnosed, being difficult to be qualitatively assessed regardless of any concurrent medical condition. Taking into consideration the multifactorial etiology of the disease, it has been suggested that there are several underlying mechanisms that, by themselves or combined, may participate to or further decrease fertility in endometriosis [4]. The complex inflammatory syndrome could be partially responsible for the sub or infertility, as it associates and determines profound alterations, such as anomalies of peritoneal fluid and local environment, pelvic anatomy, ovaries and uterine cavity [5]. The adherence syndrome, because of both endometriosis and related to surgical treatment, pelvic pain and dyspareunia, and their combined negative impact on sexual function, additionally reduced fertility [6]. Concurrent adenomyosis, often underdiagnosed and unheeded, which shares biological and molecular features with endometriosis, is believed to complicate even more both fertility and pregnancy's outcome [7]. Assessing mechanisms and processes that could further decrease fertility is of major importance regarding patient's reproductive status and may impact disease management.

Materials and Methods

A research of the literature was conducted in the databases of PubMed and EMBASE, to select full-length English articles published in medical journals up to October 2022. Research has been focused on underlying mechanisms and abnormal processes that may influence fertility of women diagnosed with endometriosis, except

iatrogenic infertility and regardless of stage and treatment. The aim of this review was also to point out negative factors that could additional impair fertility, by themselves or combined, such as the impact of pelvic pain, sexual function and concurrent adenomyosis on preexisting fertility anomalies related to endometriosis. Not least, it has been under attention the conditions in which abnormal mechanisms may additionally impact one another to further decrease fertility and related quality of life. The keywords included in the search strategy were endometriosis, fertility, Antimullerian hormone, inflammation, adherences, pelvic pain, sexual function and adenomyosis.

Results

Endometriosis - Background

First introduced in the medical nomenclature by Sampson in 1927, endometriosis has been a challenge to researchers as concerns etiology, pathogenesis, genetics and treatment. History of endometriosis dates long before, and several scientists have tried to describe the condition and to contribute to its etiology and pathogenesis. Over the years, many theories were postulated in order to accurately explain the characteristics, dissemination, stages and related complications of the disease [1,8]. Several mechanisms are accepted towards nowadays, although none of them may be entirely responsible for all endometriosis locations [9]. They may be divided into three major groups. First, retrograde menstruation though the fallopian tubes or mechanical transportation of the endometrium cells by blood and lymphatic vessels during invasive or surgical procedure are widely accepted mechanisms of occurrence. A second group, also known as the coelomic/metaplasia theory, relates to in situ growth of endometriosis lesions from ectopic cells developed in early intrauterine fetal stage. At last, the induction theory is centered on the capacity of endometrial cells, deriving from endometrial cavity, to incite the epithelium of the peritoneal cavity to develop into endometrial foci [3,10,8]. Together with immune abnormalities, all previous theories have tried to explain the variable and complex nature of the disease. Despite years of continuous and sustained research, endometriosis remains a challenge and an enigmatic medical condition, considered to be the result of a series of abnormal biological processes [2].

Endometriosis is a chronic, estrogen dependent, progesterone resistant and inflammatory disease. The medical condition affects up to 10% of general population, but the incidence is difficult to be determined, especially in early stages when symptoms are mild and non-specific [11]. Among women seeking medical care for chronic pelvic pain, the diagnosis of endometriosis rises to up to 80%. The prevalence is also increased among female with subfertility or infertility and which require Assisted Reproductive Techniques (ART), and is considered to be up to 50% [5]. It is briefly defined as the presence of endometrium stoma and glands or endometrial tissue outside the endometrial cavity of the uterus. Endometrial implants are commonly diagnosed within peritoneal cavity, but extra peritoneal foci may be found disseminated throughout the body [12]. Most frequently, endometriosis lesions are located in the pelvic compartment, such as peritoneum, ovaries, rectovaginal space, but also the bowel, bladder, ureters, abdominal wall and nerve matrix may be involved, particularly as the disease progresses [13]. Extra pelvic locations have been documented and disseminated endometriosis may be found at any site throught the organism, as in diaphragm, lungs, pleura or even the brain. The clinical symptoms reported by patients vary highly and depend on involved organs [14]. Most frequently, women seek medical attention due to the pain syndrome related to endometriosis, especially chronic pelvic pain, dysmenorrhea and dyspareunia, but also for the sub or infertility that endometriosis frequently determines. Also, considering concurrent involvement, patients may recall dyschezia, non-cyclic pelvic tenderness and pain, and other organ-specific symptomatology [15,16]. Depending on disease's clinic and associated complications, women often develop increased levels of stress, decreased self-esteem, anxiety, depression and highly impaired quality of life [17]. Subsequent infertility plays an important role in well-being of patients, considered to both negatively influence and induce psychological anomalies. It often leads to impaired social, financial, professional and relational status, turning endometriosis into a complex, multifactorial disease that is difficult to manage [18,19].

Many efforts have been done regarding a classification of endometriosis, as stages may or should characterize symptoms, associated complications, appropriate treatment and management, and predict fertility anomalies. Based on involvement of peritoneum, ovaries and deep endometriosis, today there are several classifications that are often combined in order to properly assess the disease. Regarding fertility, extensive research bas been done in order to properly provide an accurate classification and prognosis. Out of the numerous protocols developed, three are commonly used for both disease extension and fertility prognosis, namely revised American Society for Reproductive Medicine, Endometriosis Fertility Index or Enzian classification. As for the reproductive status, Endometriosis Fertility Index is considered to have the highest predictability and prognosis. Nevertheless, we should have in mind the complexity of endometriosis and each case should be uniquely evaluated for extension, treatment management and fertility [20,21].

Impact of Endometriosis on Fertility

For a reproductive age woman, fertility and procreation are considered very important aspects. Thus, subfertility or the loss of fertility may have a significant negative impact on quality of life [22]. If this occurs concomitant, or as a consequence, with other debilitating medical conditions, such as endometriosis may present, it is considered both psychologically and socially devastating. It may be considered highly stressful and determines levels of depression comparable to other major health diseases and twice as high compared to normal population [2]. Considering endometriosis, the psychological impact of related fertility issues is of great importance to be properly assessed. Also, fertility management should be directed towards preserving fertility [23]. When considering fertility in patients with endometriosis, paraclinical evaluation should to supplemented by the others, particular aspects, that may furthermore negatively impact fertility. Several conditions related to endometriosis will be discussed, such as inflammatory syndrome, sexual function and concurrent adenomyosis. Their underlying mechanisms may contribute the pathophysiology of the decreased fertility rate among patients diagnosed with endometriosis.

Ovarian biomarkers and fertility evaluation

In order to evaluate the ovarian function, both endocrine and fertility potential, there are several biomarkers and imaging techniques available. A quantitative assessment may be easily performed and is based on ovarian biomarkers. Those markers are divided into static, dynamic and ultrasound parameters [24]. Paraclinical biomarkers, such as estradiol, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Inhibin B, Antimullerian Hormone (AMH), are widely available and reflect ovarian function throughout the menstrual

cycle [25,26]. Apart from AMH, the static ovarian markers may vary and depend on the menstrual phase or concurrent medical conditions, so the evaluation should be integrated into the clinical context for an accurate assessment. AMH, also a static ovarian marker, is a dimeric glycoprotein and is included in the transforming growth factor beta family. The hormone is secreted by granulosa cells within the ovaries, regardless of the menstrual cycle phase, and is closely associated to the number of antral follicles and ovarian reserve [27,28]. It is currently the most accurate and widely used paraclinical marker in a variety of gynecological and reproductive medical conditions. It can reflect the endocrine function, quantitative ovarian reserve, as well as the damaging effect of cancer treatment and gynecological surgery upon the ovarian tissue [29]. The dynamic markers of the ovarian function include ovarian stimulation tests (as clomiphene citrate based), gonadotrophins and gonadotrophins releasing hormones (GnRH) analogues. They assess the endocrine response of the ovaries to controlled stimulation and may predict the current function [30]. Together with laboratory parameters, ultrasound imaging techniques are frequently included in both quantitative and qualitative assessment of the ovarian function. Antral Follicle Count (AFC) and ovarian volume are commonly performed during early follicular phase and they closely relate to endocrine function, to the response to controlled ovarian stimulation, as well as to AMH serum levels. The decline of those parameters, AFC and serum AMH, may predict ovarian ageing, premature ovarian failure (more accurately before 45 years of age) and fertility potential [31,32]. In addition to quantitative evaluation, fertility requires a qualitative assessment of both endocrine function and genital organs anatomy (uterine cavity and adnexa). There is no standardized protocol for fertility potential evaluation, although many efforts are made towards [33]. Even though paraclinical biomarkers and ultrasound techniques may accurately reflect the endocrine function, they have a low sensitivity regarding future fertility, as pregnancy's number and outcome [34].

Inflammatory syndrome of endometriosis

The inflammatory syndrome related to endometriosis may be partially responsible for the sub or infertility that associates the condition. The mechanisms that are believed to be involved in the inflammation that determines endometriosis are difficult to be entirely confirmed and assessed, but research towards its etiology and specific treatment are of great importance and may decrease both the symptoms of endometriosis and the fertility issues that come as a consequence of this enigmatic disease [5,35]. Although not completely elucidated, the underlining processes that determine endometriosis infertility may relate to adhesions and anomalies of the pelvic anatomy, abnormal peritoneal and ovarian function, and dysfunctions of the eutopic endometrial receptivity. They are the endpoint of an abnormal immune function, leading to a heterogenous growth and progress of the disease [6]. Back flow or retrograde menstruation of cells deriving from uterine cavity is common during menstruation in approximately 90% of women, but the physiological process results in apoptosis and elimination of those cells by the immune system [10]. Yet, it is important to be acknowledged that in patients diagnosed with endometriosis, there are different influences and abnormal mechanisms that stimulate and support the endometrial implants to invade, survive and proliferate regardless the ectopic location. Studies, however, report an increased frequency with a shorter interval between menstruations, as well as a higher volume as a consequence, more menstrual endometrial cells translocated into peritoneal cavity [16]. Also, there has been described an increased activity of estrogen receptors and inhibited progesterone receptors. Those decrease immune response and impede apoptosis within the endometriosis foci [36,37]. The ectopic endometriosis implants are under the same cyclic hormonal influence as eutopic endometrium, but, in addition, they are characterized by neo-angiogenesis, neurogenesis, and increased production of collagen and fibrogenesis [3]. Together with anatomical alterations, they determine chronic inflammation and pain syndrome related to endometriosis. Apparently, there is a two-way influence of the underlying mechanisms and the progression of both endometriosis and associated sub/infertility [38]. When discussing infertility in this enigmatic medical condition, it is critical to point out the anomalies of peritoneal environment, pelvic anatomy, ovaries and uterine cavity induced by endometriosis. They are to be assessed separately below. In addition, the impact of chronic pelvic pain, impairment of sexual function and concurrent presence of adenomyosis, may additionally decrease fertility.

Peritoneal cavity

The peritoneal fluid of peritoneal cavity, in which are contained pelvic and abdominal organs, highly depends of menstrual cycle phase in the matter of both volume and composition, due to increased permeability related to estrogen influence [5]. It is mainly composed of electrolytes, urea, endometrial cells, steroid hormones, and components of immune system and blood flow, such as macrophages, lymphocytes and erythrocytes, cytokines, angiogenic and growth factors, and others [22]. The concentration of this component is related to cell's activity and secretion, and have a great impact on the peritoneal cavity environment. An altered proportion of those elements leads to an abnormal environment and this altered peritoneal fluid exerts a negative impact on anatomy and organs function [10,39]. In women with endometriosis, both volume and concentration of the components are modified. The volume is higher compared to normal population, especially in patients addressing for infertility [40]. It's elements also present abnormal concentrations and cellularity, thus creating an immunotolerant surrounding for endometriotic foci to survive and progress. The altered peritoneal fluid is particularly influenced by the endocrine secretion of endometriosis implants, especially estradiol, progesterone, growth factors, proinflammatory cytokines, such as interleukin 1, 6 and 8, as well as monocyte chemoattractant protein, tumor necrosis factor, and many others. Also, there is a decreased activity of natural killer cells and increased of both number and function of Proinflammatory cellular activity. This pathological peritoneal environment determines the exposed endometriotic cells to further proliferation and development, and therefore leads to progression of local endometriosis [5,41,42].

Various studies have tried to select the exact abnormal cellularity related to endometriosis peritoneal fluid components, in particularly cytokines pathognomonic to the disease, but this altered immune profile has been challenging to be described. There were identified various interleukins (1ra, 1b, 6, 8 10, 16), growth factors, granulocytes- colony stimulating factors, monokines, chemokines, oncogenes and proto-oncogenes [35]. Also there seems to be an increased insulin-like growth factor, cyclooxygenase 2 and prostaglandin activity and expression in the peritoneal environment of patients. Related to endometriosis abnormal humoral immune activity, a series of autoantibodies have been also identified and considered to play an important role in local disease and associated infertility [43]. Overexpression of macrophages, cytokine lymphocyte B stimulator and their production of autoantibodies states towards considering endometriosis more

likely an immune mediated disease, being known that it may associate or be associated with other autoimmune diseases [44,45]. Among identified autoantibodies related to endometriosis, we can mention anti endometrial, antinuclear, anti-DNA and antiphospholipid antibodies. In relation to them, an inhibition of transferrin activity as a consequence, an elevated iron level, is associated to increased oxidative stress and abnormal local processes of injury and repair [46]. Although numerous abnormalities have been identified over the years, up until now there is no evidence regarding a specific, hopefully pathognomonic, marker or series of marker to be routinely recommended to be determined in order to properly assess endometriosis. Yet, it is important to comprehend that alteration of peritoneal fluid composition and concentrations of components has a deep impact on pelvic organs. The proinflammatory environment associated to previous anomalies is reflected in increased oxidative processes and profound alterations of anatomy and physiology [47,48].

Fertilization, a process that occurs in the fallopian tube ampulla, is affected due to direct exposure to an abnormal peritoneal fluid. The proinflammatory components influence both oocytes and sperm. They interfere with the binding and fusion between oocyte and sperm, especially related to abnormal TNF, IL-1, and macrophage inhibiting factor activity. Also, they are associated with DNA damage and apoptosis of the sperm. In addition, increased iron affects both the maturation of ovarian glanulosa cells and impair the motility of the sperm [5,49]. Although numerous proinflammatory cells have been incriminated to influence endometriosis occurrence and progression, studies have further tried to identify if some may be more frequently associated to infertility. A series of 11 cytokines, namely IL 5, 9, 13, interferon a2, chemokines, monocytes chemoattractant 1 and 3, macrophage colony stimulation factor, stem cells growth factor b and leukemia inhibitory factor were particularly associated to endometriosis induced infertility. Apparently, the negative environment is a result of an abnormal lymphocyte Th 1 and 2 [5,35]. Nevertheless, despite the continuous research regarding the abnormal cytokine's concentration and activity, there is still a debate on whether this cellular expression is the cause or a consequence of endometriosis [1,3].

Pelvic Adherences

Pelvic adhesions develop is the pelvic area as bands of connective tissue among anatomical structures are further impair both anatomy and function or involved organs. Commonly, they are the consequence of various pelvic infections, inflammatory syndromes and following pelvic surgery [8,50]. Active endometriosis is considered to be the leading cause of non-surgical occurring adherent syndrome, and is related to local and systemic inflammation as integrated part of this medical condition. The underlying mechanisms of adherence's occurrence and growth are still not completely understood, but inflammatory syndrome, anomalies in tissue wound and repair processes, and surgical injury combine in the development [6]. Also, abnormal immune response, with modified presence and levels of proinflammatory cytokines and factors associated with angiogenesis and growth, will most probably favor adherences in endometriosis, with or without surgical treatment. Regarding possible immune involvement, research attribute the major role for endometriosis adhesive syndrome to cytokine IL1a and b mainly 1b [51].

Considering classification and stage of endometriosis, the adherences have various types. They can appear transparent and thin, and throughout disease progression can develop into thick, opaque and dense. Also, they may go from mild to frozen pelvis, in which the whole pelvic area is affected [5]. Most frequently, they involve internal genital organs and adjacent structures. Fibrotic band interconnect adnexa, fallopian tubes, uterus, bladder, anterior abdominal wall, vesico-uterine and Douglas' pouch, uterosacral and round ligament, colon, small intestines, as well as rectovaginal septum and the omentum [52]. The interdependence between adhesions formation and endometriosis stage has been under great concern, as well as the reoccurrence of adhesions following repeated surgery for the treatment of the disease. The prevalence is reported quite different by studies, ranging from 37,6 to 74 % at first laparoscopy, to up to 82% after repeated surgical interventions. This concludes that surgical treatment negatively corelates to both formation and severity of the adhesion syndrome of endometriosis [5,53]. Pelvic adherences, as a consequence of both endometriosis and related surgical treatment of endometriosis, associate a series of complications. Pelvic pain, dyspareunia and constipation are the leading symptoms that impact quality of life and complicate associated subfertility or infertility. Further impact of pain and dyspareunia on sexual relations additionally reduces fertility [54].

Pelvic Pain

The leading symptom of endometriosis is represented by chronic pelvic pain, which is also the main concern of women addressing medical care. More than 60% of women seeking for chronic pelvic pain are diagnosed with endometriosis, but the symptomatology is characterized by profound heterogenicity and doesn't corelate to the severity of diagnosed lesions [38]. Often the primary symptom, pain is considered to proceed endometriosis diagnosis with up to 8 years ahead. This is related to the non-specificity of endometriosis early clinical symptoms. Also, despite the variety of non-invasive diagnostical methods, the certainty diagnosis is based on direct visualization only during laparoscopy or laparotomy, and histopathological exam [3,15]. Even though there should be a direct correlation between severity of pain and stage of endometriosis, it appears that the previous two parameters are not necessarily directly proportionated [5,16]. There is much concern regarding etiology of endometriosis induced pelvic pain, given the impact of chronic pain on social, economic, sexual and personal relationship, and quality of life of patients. Also, the negative impact is additionally enhanced by associated comorbidities, such as dysfunctions of the bladder and bowel [55]. The concomitant medical conditions, often presenting as autoimmune disease (overreactive bladder, interstitial cystitis or irritable bowel), suggest a more complex etiology of endometriosis and related chronic pain, most probably generated or derived from immune system dysfunctions [56]. Etiology of pelvic pain can also be concomitant or, sometimes, originate from the inflammation and dysfunctions of adjacent pelvic organs, altered by the systemic syndrome of endometriosis [13].

Endometrial foci or lesions and adherence syndrome is among the most incriminated underlying mechanisms for endometriosis related pain. Inflammation of the uterus and abnormal composition and activity of peritoneal fluid, as well as the cyclical bleeding from ectopic lesions and the proinflammatory environment from both endometriotic foci and peritoneal fluid contribute to pelvic pain [57]. The subsequent inflammation of pelvic sensorial nerves may additionally increase the symptoms. Furthermore, studies suggest that continuous abnormal cytokine concentration and activity will lead to an activation and sensitization of nerve fibers within the

endometriosis implants and translocate the peripheric pain into central pain. The pain transfer to central nervous system will be crucial and related to non-menstrual pelvic pain and other, subsequent, chronic visceral pain [58]. The pathogenesis of endometriosis related pain is based on extensive research regarding the angiogenesis and neurogenesis that are associated. Pain is transmitted and processed by the central nervous system throught peripheric pathways [35]. In endometriotic lesions, for the ectopic cells to adhere and develop, there is an increased angiogenesis and other growth factors that will further support the growth and progression. Together with angiogenesis, there is an increased neurogenesis, both supported and stimulated by high levels of estrogen and abnormal immune system, known to be iconic in endometriosis [8,36]. This results in abnormal and elevated density of blood vessels and nerve fibers, nerves that are unmyelinated and act like nociceptors. Furthermore, neuroangiogenesis has a negative impact on local, preexisting nerve fibers, stimulating their invasion and inflammation [59,60]. The nerve density and pain intensity are directly proportional with disease progression, also corelated to elevated estrogen, as the disease is characterized. Studies suggest that, for a superior pain management, the endometriotic lesions should be inhibited or surgically removed before the onset of a highly dense and complex nerve fiber network. Hereupon, following surgical treatment up to 28% of patients will not have a reduction of clinical symptoms, whilst others will start experiencing pelvic pain within the first 12 months even without a confirmed reappearance of endometriotic lesions. This may also be related to adherences frequently occurring after surgery [51,61]. Those mechanisms can explain the intensity of endometriosis associated pain syndrome, confirming both the local inflammation and the increased density of the new nerve network that has been confirmed around endometriotic implants and lesions [62].

In addition, there has been suggested a neurologic inflammation, a peripheral and central sensitization. They are dependent of proinflammatory cytokines, especially IL 1b responsible for chronic inflammation, as well as for chronic visceral pain and hyperalgesia described in endometriosis [63,64]. Central sensitization can also be observed in other inflammatory conditions and it is considered to be responsible for chronic pain due to sensitization of central nervous system neurons and hyperexcitability, as well as developing alterations in processing and memory of pain. Together with them, cross-organ sensitization may have an additional contribution to endometriosis related chronic pain [65,66]. The phenomena develop when a sensitized organ induces sensitization to the nerve afferents of an another, adjacent organ, located in proximity. Research has been conducted towards identifying the exact mechanisms for the cross-organ influence is unclear, but the activity and stimulation of local environment, abnormal immune system, angiogenesis and neurogenesis may all have a contribution to the end-point effect [67]. Despite pathogenesis of pelvic pain, it is crucial to take into consideration the impact of pain syndrome on young women diagnosed with endometriosis on fertility or to the pathogenesis of fertility abnormalities. The pain syndrome, as described above, may be not related to disease staging, but can associate severe psychological anomalies and contribute to infertility, often related to impaired sexual function and decreased quality of life. The devastating impact of chronic pelvic pain on sexuality is widely known together with general aspects of inflammatory syndrome of endometriosis, determines profound physical and psychological alterations that contribute to infertility.

Ovaries

The presence of endometrioma has a double negative effect on ovarian function. It affects it structurally by occupying space and further destruction of the adjacent normal ovarian tissue. Also, because of abnormal cytokine expression, it impairs fertilization and oocyte quality [68]. The content of endometrioma is rich in proinflammatory cytokines, such as IL6 and 8, iron, growth factors, metalloprotease, as well as reactive oxygen components. Their surrounding diffusion is associated with local inflammatory environment and oxidative stress, and leads to tissue anomalies such as fibrosis, decreased stroma and follicles number, and increased atresia of small follicle [49]. Within the ovarian stroma, abnormal processes associated to the presence of transforming growth factor b1 and reactive oxygen species may be observed, inducing myofibroblast transformation and stimulating fibrosis and formation of adhesions. This process will additionally determine loss of stroma and will negatively impact ovarian blood supply, with further decrease in follicular growth and development [1,3,5].

Among the cytokines associated to endometriosis, studies have identified the increased follicular concentration of IL 1b, 6, 8, 12 and 18 seem to be most frequently associated with detrimental effects on fertilization [69]. Elevated IL 1b and 6 decrease pregnancy rates, while IL 8 and 12 negatively impact oocyte quality and maturation. In addition, cytokine abnormal expression impacts the function of G regulating estrogen receptor, which plays an important role in estrogen signaling and follicular development. A decreased level of this receptor may be responsible for a low follicular expression in ovaries affected by endometriosis [72,73]. Also, the local presence of myeloperoxidase and oxidative stress further impairs oocyte quality and patient's fertility, especially in moderate or severe forms of endometriosis [5]. Even though those abnormal findings associated to endometriosis have been confirmed to be present in all pelvic area, ovarian cortical anomalies are more severe in ovaries with endometriomas compared to contralateral, unaffected ovary. Moreover, the association of ovarian endometrioma and deep-infiltrating disease additionally decreases both ovarian reserve and oocyte quality [53,73].

Uterus

There is a great concern regarding the impact of endometriosis upon implantation rate. Apart from the confirmed negative impact related to oocyte's quality and fertilization, additional inflammatory environment inside the uterine cavity and other endometriosis-associated processes could further impair fertility [74]. Morphologically, the endometrium of a patient with endometriosis is identical to a woman without, but apparently there are alterations and profound abnormal processes underlying. At first, hormonal response should be taken into consideration. Endometriosis is an estrogen dependent disease characterized by resistance to progesterone. Commonly, progesterone acts in a pro inflammatory manner at the end of secretory phase and determines the rise of cytokines, reactive oxygen species and prostaglandins, mechanism that induces menstruation [37,75]. Because of abnormal progesterone resistance in women with endometriosis, the concentration of previous inflammatory cells occurs earlier during secretory phase. In addition, in the eutopic endometrium of patients diagnosed with endometriosis, there were observed impaired processes in gene expression of Proinflammatory cells, with increased of chemokine and cytokine production, abnormal DNA- methylation, and alteration in the physiological apoptosis, adhesion and healing

restore following traumatisms [36,76]. Associated to increased local estrogen activity determined by increased activity of P450 aromatase, as well as the presence of immature natural killer cells within the uterine cavity, it results in an abnormal uterine implantation of a fertilized egg and decreased fertility rate [22,23]. Several studies have tried to evaluate the implantation rate following IVF techniques, but results have been contradictory in some points, leading to the conclusion that clinical pregnancies in patients with endometriosis may be related to a decreased number of oocytes retrieved and fertilized [53]. Also, other studies have tried to identify differences among transcriptional genes related to endometrial implantation and receptivity, yet some found no significant anomalies. Therefore, despite contradictory conclusions, alteration of both anatomy and function of eutopic endometrium in patients with endometriosis and seeking for infertility, should be evaluated at a larger scale and integrated with the other associated anomalies for a better management [77,78].

Sexual Function and Endometriosis

Sexual function and reproduction are considered to be important aspects in women's life. Sexuality has tried to be defined along years as a state of emotional, anatomical, psychological and social well-being, associated with sexual desire, not necessarily in the absence of a medical condition. It is highly dependent on various factors; therefore, it is not a pure physic phenomenon. Sexual dysfunctions vary among population, considering age, associated medical diseases, treatments and gynecological conditions [79]. As mentioned before, chronic inflammatory syndrome of endometriosis associates pelvic pain and adherences, that are common causes for developing dyspareunia and sexual dysfunctions [80]. Compared to young healthy women, patients diagnosed with endometriosis experience much more severe symptoms. Both intensity and frequency are considered to be related to personal characteristic, pain perception, and stage of the disease [13]. Nowadays, endometriosis is considered to be a social and economic issue also. Patients struggle for years both before and after the diagnosis of endometriosis has been established. The impact of chronic pain, dysmenorrhea, reduced performance at work and financial problems related to costs of disease's treatment and infertility, additionally decreases self-esteem and quality of life [57]. There is a two-way negative influence between dyspareunia, and related sexual function, and sub/infertility in endometriosis [81].

Endometriosis determines systemic anomalies affecting gonads are adjacent organs. Chronic pelvic pain, with its abnormal central perception, distortions of pelvic anatomy and adherences, neurogenesis with increased nerve density and inflammation, determine dyspareunia and sexual dysfunctions. Dyspareunia, the pain during intercourse, is particularly determined by endometriosis, especially profound type, but also superficial [82]. For superficial dyspareunia or pain of the vulva and vaginal introitus, the mechanisms involved are related to inflammatory syndrome and pain perception. Profound dyspareunia seems to be particularly proportionate to the deep, infiltrative stage of the disease. It is not uncommon for patients to experience both types, leading to severe clinical symptoms [83]. They reflect in physical pain and frequency of sexual intercourse, desire, achieving orgasms, and overall personal and intimate relations. There have been several studies that assessed sexual quality of life in patients diagnosed with endometriosis, and all confirm decreased results for both superficial and deep dyspareunia. Lower scores were associated with the deep type, probably related to infiltration of rectovaginal septum, severe inflammation and adherences [54,84]. Also, dyspareunia may be exacerbated by adjacent organ involvement due to endometriosis, such as bladder, intestines and rectum. Often, the end-point for patients is to avoid sexual intercourse, furthermore affecting already impaired fertility, and deepening depression [85]. Fertility anomalies associated to endometriosis have a high negative effect on women's quality of life and additionally amplify severity of endometriosis symptoms through various general and psychological mechanisms. There has been extensive research and studies confirm that infertility has a major impact on women's life and quality of life, often comparable with other life-threatening medical conditions, especially when concurrent to diseases that impact every-day life and personal relationships [86]. In endometriosis, sub or infertility and related depression is known to affect sexual function and sexual quality of life [17].

Concurrent Adenomyosis and Fertility Impact

Endometriosis may be related to several other medical conditions, some may be contributing to fertility status of diagnosed patients. Out of them, when considering fertility and pregnancy outcome in endometriosis, one aspect that should also be taken into consideration, namely the presence of concurrent adenomyosis. Difficult to diagnose, because the confirmation is based on histopathological report, adenomyosis is believed to share biological and molecular features with endometriosis, some reporting that the two entities belong to the same medical condition, but express different clinical stages and features [87].

Adenomyosis is benign medical condition, estrogen dependent, characterized by the presence of endometrial glands and stroma inside the uterus myometrium, that may appear in a focal or diffused pattern. Most probably appears as a consequence of an abnormal invasion of muscular layer of the uterus though the junctional zone that separates endometrium from myometrium [88,89]. To the process it is thought to participate an altered immune response, particularly related to tissue injury/repair mechanisms, and a modified immunological environment, overexpressed in proinflammatory cytokines, within the uterine cavity. As for endometriosis, the etiology of adenomyosis is multifactorial, but consequences are serious and complications additionally reduces fertility and pregnancy outcome [7].

The incidence of the disease is often difficult to be determined, considered to be found in 20 to 35% of women. Incidence also rises with age and parity, and frequently determines abnormal uterine bleeding, dysmenorrhea and dyspareunia. It associates with uterine myoma and endometriosis, especially over 40 years of age, but it has been described to be present in younger women before the age of 30 [90]. The concurrence with endometriosis is particularly important in women of reproductive age patients, reported in up to 21.8% of cases and higher when severe dysmenorrhea and deep infiltrating endometriosis are present. The underlying mechanisms that reduce fertility are various, related to both local, intrauterine anomalies, and clinical symptoms [91]. The uterus of a patient diagnosed with adenomyosis is characterized by thickening of the myometrium, altered distensibility, hypercontractility and distortion of the cavity [87]. Also, abnormal intrauterine immunological environment, enriched with proinflammatory cytokines, reactive oxygen species, prostaglandins, and others induce anomalies in uterine contractility, endometrial receptivity and altered nidation, and impact sperm motility and transport [92,93]. Those mechanisms impact fertility through reducing clinical pregnancies, early pregnancy loss, but especially by diminishing the pregnancy's outcome [7]. Also, because of abnormal trophoblast

invasion and placentation, it has been confirmed that adenomyosis associated obstetrical complications, such as preterm delivery and rupture of membranes, fetal growth restriction, placental anomalies, namely placenta previa and placental abruption, as well as pregnancy hypertensive disorders [94,95]. Anomalies have been confirmed by studies regarding in vitro fertilization procedures in patients with endometriosis and concurrent adenomyosis [96]. Although adenomyosis induces profound and important alterations upon anatomy and function of genital tract, it is difficult to evaluate the extent in which it affects fertility. Nevertheless, the association between the two conditions have been proven to have a detrimental effect on patient's reproductive status, with additional physical, psychological, social and financial complications [97].

Conclusion

Despite extensive research, endometriosis is still considered an enigmatic disease and with a multifactorial pattern. Aside from clinical manifestations, that often delay the appropriate diagnosis and disease progresses, the underlying mechanisms determine extensive anomalies to the pelvis and beyond. One major concern when diagnosis is confirmed, is the negative impact that endometriosis induces upon the reproductive status. Fertility issues associated with endometriosis are difficult to be properly assessed due to profound alterations of the genital tract. Anomalies of peritoneal fluid and local environment, often related to the inflammatory syndrome of endometriosis, exert damage on pelvic anatomy, ovaries, such as reduced ovarian reserve and impaired oocytes quality, and uterine cavity, with decrease of implantation and pregnancy rate. In addition, the adherence syndrome, chronic pelvic pain and altered sexual function may deepen the preexisting fertility anomalies. Concurrent adenomyosis additionally reduces clinical pregnancies, determines early pregnancy loss and impacts pregnancy's outcome. In conclusion, assessing mechanisms and processes that could decrease fertility, as well as emphasizing the correlation established between them, is of great importance in the management of endometriosis induced infertility and patient's quality of life.

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