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ENDOMETRIOSIS: WHAT ARE THE MECHANISMS RESPONSIBLE FOR INFERTILITY?

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ABSTRACT:
INTRODUCTION: ENDOMETRIOSIS IS ONE OF THE MOST IMPORTANT CAUSES OF INFERTILITY IN REPRODUCTIVE AGE PATIENTS, BUT WHAT ARE THE MECHANISMS INVOLVED? THIS ARTICLE DESCRIBES STEP BY STEP THE PSYSIOPATHOLOGY BACKGROUND THAT LEADS TO PREGNANCY ACHIEVING IMPAIRMENT.
METHODS: WE PERFORMED A REVIEW OF THE INTERNATIONAL SPECIALTY LITERATURE.
RESULTS: ENDOMETRIOSIS DETERMINES MODIFICATION OF NEOANGIOGENESIS AND CELLULAR MEDIATED RESPONSE BY HIGH CONCENTRATIONS OF INFLAMMATORY CYTOKINES (IL1, IL6, TNF ALPHA, PROSTAGLANDIN, PROTEASES) AND ANGIOGENIC FACTORS (IL8 AND VEGF). THESE CAUSE ALTERATION OF THE PELVIC ANATOMY AND, IN ADDITION TO LOWERING AVB3 INTEGRIN ADHESION MOLECULE AND THE L-SELECTIN LIGAND, CONTRIBUTES TO ASSOCIATED IMPLANTATION FAILURE. NEVERTHELESS, OVULATION IMPAIRMENT BY MECHANICAL DISTRUCTION OR ALTERATION OF GRANULLAR CELLS FUNCTION WITH ESTROGEN AND PROGESTERONE SECRETION DEFICIENCY AND LUTEAL PHASE MODIFICATIONS HAVE A FERTILITY NEGATIVE IMPACT. THE EMBRYOTOXICITY EFFECT COMES IN ADDITION TO THIS WITH AN INCREASED ABORTION RATE. ALTERATION OF SPERMATOZOA MOBILITY AND ENDOMETRIAL RECEPTIVITY, INCREASED UTERINE CONTRACTILITY AND FALLOPIAN TUBES OBSTRUCTION COMPLETE THE PICTURE OF INFERTILITY IN THE ENDOMETRIOSIS PATIENT.
CONCLUSIONS: ENDOMETRIOSIS AFFECTS FERTILITY THROUGH MULTIPLE MECHANISMS, AND IN ORDER TO TREAT AND GET PREGNANCY IN THESE PATIENTS, IT IS NECESSARY TO UNDERSTAND THEM.

KEY WORDS: ENDOMETRIOSIS, INFERTILITY, IMPLANTATION, EMBRIOTOXICITY, *INFLAMMATORY CYTOKINES.*

INTRODUCTION

Infertility poses more and more negative impact in the modern society, both by the psychical effect upon the couples, but by the social and financial society implications as well, as the rate of natural increase is negative in many developed countries, and in Romania it has been negative for many years now. This determines population aging, with fewer young working people that can support the elderly, with negative financial impact on the society. In addition to this, endometriosis patients suffer from frequent severe pain episodes that prevent them from working, affects their personal and professional relationships, nevertheless causing them fertility problems as well[9].

Recent studies demonstrate that almost 50% of infertile women have endometriosis and that 30-50% of endometriosis patients are infertile[10]. Endometriosis is a chronic disease present in 6-10% of fertile aged women[11], that alters fertility due to alteration of all reproductive system

[9] Mehedintu, C., Bratila, E., Antonovici, M.R., Brinduse, L.A., Berceanu, C. and Roman, H., Use of the sf-36 general health status survey in health-related quality of life assessment in patients with colorectal endometriosis.
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components[12]. By simply comparing the pregnancy rates (PR) we can observe the differences: PR per month in normal couples is 15-20 %[13], and in endometriosis patients, the monthly PR is 2-10 %[14].

OBJECTIVE

The exact physiopathological mechanism is not yet completely established[15], but there are many well known modifications related to endometriosis[16]. In order to be able to treat these patients we must take into account its physiopathology and in this paper we studied the international specialty literature and we will present the findings.

MATERIALS AND METHODS

This paper is a review of the international specialty literature regarding the physiopathological mechanisms of endometriosis that determine infertility, including cohort studies and reproductive societies guidelines (ESHRE, ASRM).

RESULTS

Inflammation and infertility

Endometriosis patients have been shown to have a larger amount of peritoneal fluid containing significant concentrations of inflammatory cytokines such as IL1, IL6, TNF alpha and angiogenic factors such as IL8 and VEGF[17], causing alteration of neoangiogenesis and cellular mediated response[18]. These may affect the fallopian tubes, the oocyte function, the embryo and even the sperm. First of all, we must understand why this aspect is clinically important. Peritoneal inflammation leads to the modification of the pelvic anatomy[19], it influences the tubal peristalsis[20]

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and creates adhesions that affect the permeability of the salpinges[21], can impair oocyte release and inhibit ovum pickup or disturb ovum transport[22].

Non-invasively, the peritoneal fluid can be visualized by ultrasound, CT scan or MRI examination, or its presence can be indirectly presumed in case of diagnosing other endometrial lesions. The first investigation to perform, after clinical examination[23], is ultrasound examination[24], but this detects basically only endometriomas or adenomyosis. Transvaginal ultrasound can detect hydrosalpinx as well, when tubal obstruction is present and fluid builds up in the salpinges. To determine modifications of normal anatomy in endometriosis patients that can lead to infertility[25], there are additional investigations that must be performed, in order to have a correct surgery indication if necessary[26]. Sonovaginography with ultrasound gel is a useful investigation in detecting endometriotic lesions in the posterior pelvic compartment[27] that usually are accompanied with tubal obstruction and ovulation impairement. Sonovaginography with ultrasound gel, in case of endometriotic lesions of the uterosacral ligaments has a 78.5 % sensitivity and a 96 % specificity. In addition to this, endometriosis in the vaginal and rectovaginal wall[28] can be diagnosed with a very good sensitivity (79%, respectively 94%) and a specificity of 99%, respectively 97%. In regards of the Douglas pouch, were very frequently endometriosic adherences are present, the sensitivity of the method is 81%, and it can diagnose rectosigmoid endometriosis with a 94% sensitivity. Lower sensitivity (64%) of sonovaginography with ultrasound gel has been observed in detecting urinary bladder lesions[29] and not to forget, special attention must be considered in case of possible urinary tract anomalies[30]. Another important investigation in endometriotic patients is Magnetic Resonance Imaging that can be improved by Computed

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Tomography Based Virtual Colonoscopy for better accuracy of assessment in colorectal endometriosis[31].

Endocrine dysfunction, follicle development and steroidogenesis

Secondly, ovulation is affected either by ovarian endometriomas that destroy the follicular reserve or by altering the function of granullar cells. The ovarian reserve markers are affected is the endometriosis patients, it has been shown that these patients have lower AMH and higher FSH levels, even in the absence of any prior ovarian surgical treatment[32]. Nevertheless, endometriosis patients have statistically significantly higher proportion of AMH<1, compared with infertile patients with no endometriosis. Besides this affecting of the ovarian reserve, the function of the ovary is affected as well, with consequent follicular fluid alteration (low levels of progesterone, estrogen and androgens and increased activin concentrations[33] that prevent ovocyte maturation and stimulate growth of the endometriotic implants). It has been shown that the follicular fluid of the patients with endometriosis inhibit the proliferation of granular cells and the secretion of progesterone[34]. The dysregulation of steroidogenesis is an effect of decreasing of the expression of P450 aromatase in patients with ovarian or pelvic endometriosis[35]. Normally, the granulosa cell-derived paracrine factors promote P450 aromatase activity, that is the key enzyme of estrogen and E2 (17β-estradiol) production. Without sufficient E2, the follicular development is affected and so is the production of competent oocytes, that are able to reach mature metaphase II (MII) in order to be fertilized.

Endometriosis affect the normal steroidogenesis by modifying cell cycle, increasing apoptosis and dysregulating the molecular pathways involved. The low levels of E2 are present in preovulatory stage and at the LH (luteinizing hormone) surge, at ovulation time. Nevertheless, progesterone secretion is lower in postovulatory stage, additional affecting oocyte maturation[36] and the luteinized unruptured follicle syndrome has been discussed to be present in endometriosis as well. In addition to altered development of sex-hormones, the expression of estrogen and

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progesterone receptors is modified as well, by the pro-inflammatory citokines IL-1, IL-6 and TNF-alfa.

Endometriosis affects the follicular oxidative stress status, with reactive oxygen species that determine meiotic abnormalities and chromosomic instability, suplimentary reducind oocyte quality[37]. This is an effect of spindle dysruption, arresting the oocyte in prophase I, the cytoplasmatic and nuclear maturation being impaired[38]. The oxidative stress is the reason studies are being made about supplementation with Vitamin C and E in endometriosis infertility, with controversial finding though[39].

Oocyte maturation and spindle are affected by the high concentration of pro-inflammatory cytokines (IL-8, IL-12), found both in the follicular fluid and in the peritoneal fluid of endometriosis patients[40]. The oocyte function has been shown to be altered as well. In endometriosis women it has been observed incresed cortical granular loss and zona pellucida hardening, that affects fertilization and the ability of the embryo to undergo hatching and implantation[41]. The peritoneal fluid in endometriosis patients has high levels of products that also affect MII oocyte maturation, besides pro-inflammatory cytokines there are very-long-chains ceramides (sphingolipids) mediating through mitochondrial superoxide[42].

Endometriosis patients may have other endocrine and ovulatory disorders. Besides affected folliculogenesis and unrupted follicle syndrome, there may exist luteal phase defects or impairement of LH surge (premature or multiple surges). Luteal phase modifications or the fact that more than one LH peak may appear during a menstrual cycle[43] can be caused by the reduction of follicular LH receptors, with late LH peak and luteal phase, which prevents follicular growth, estrogen secretion and progesterone secretion[44].

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Embryo implantation

Thirdly, endometriosis affects embryo implantation. This may happen on the one hand due to the high concentrations of inflammatory factors[45] (increased number of activated macrophages, increased production of TNF-α, prostaglandin, IL-1, IL-6, and proteases), which have a toxic effect on implantation[46] and a negative impact upon the expression of estrogen and progesterone receptors. Reduced expression of progesterone B receptors, essential in decidualization, have an important role in implantation failure[47]. Inflammation also leads to increased uterine contractility, that may be a significant infertility factor[48]. On the other hand, implantation failure may be caused by lowering the αvβ3 integrin adhesion molecule[49]. Nevertheless, endometriosis impairs implantation by lowering the quality of L-selectin ligand (LSL) and by affecting LSL expression[50]. L-selectin ligand is a marker of endometrial receptivity, an endometrium expressed glycoprotein that binds to the expressed trophoblast L-selectin. Its defects thereby affect embryo attachment to the endometrium and implantation failure. Last but not least, endometrial receptivity and embryo implantation may be affected by elevated levels of IgA and IgG antibodies, autoantibodies to endometrial antigens, and lymphocytes, that have been observed in the endometrium of endometriosis women[51]. The immune system in these patients is disrupted, with high concentrations of immune cell types, such as neutrophils, macrophages, dendritic cells, natural killer cells, T helper cells, B cells[52].

Mobility of spermatozoa

In addition to these, endometriosis affects the mobility of spermatozoa. Pro-inflammatory cytokines and the oxidative stress mentioned above affect the sperm in the uterus and when travelling through the fallopian tubes[53].

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Embryotoxicity

Another important aspect is that endometriosis alters embryonic development, it can have embryotoxicity and leads to an increased abortion rate. Studies showed that the high inflammation from the peritoneal fluid, that flows in the uterus through the fallopian tubes, slows down the growth rate of the embryo, increases the apoptosis rate and the DNA fragmentation[54]. An interesting aspect is that administration of dexamethasone has shown to reduce the embryotoxic effect[55].

Immunohistochemical profile, aggressiveness and recurrence risk

Last but not least, an important aspect in endometriosis patients is how to appreciate the aggressiveness and recurrence risk of endometriosis, in order to advise the young patient how long can she wait until having a pregnancy, if she does not desire one at the moment. The clinical implications are not directly proportional with the severity of the disease, as there can be patients with acceptable pain and no urinary[56] or gastrointestinal symptoms that actually have a severe and aggressive endometriosis that in a couple of years will reduce almost to zero her chances of conceiving. Studies have been made to assess the immunohistochemical profile of endometriosis implants. The expression of anti-apoptotic markers (Bcl-2) and cell proliferation marker (Ki-67) has been linked to the progression and dissemination capacity of endometriosis[57]. Ki-67 marker has been showed to be not correlated with the stage of endometriosis, but with the aggressiveness and dissemination potential. When cell dissemination activity is high, cells become independent and affect the neighbouring tissues. This leads to important adhering process between the surrounding tissues and the anatomy of the area is altered. Bcl-2 proteins have been observed to be involved in disrupting the process of apoptosis, leading to abnormal cell dissemination. The expression of estrogen and progesterone receptors[58] is related to response of endometriosis patients

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to treatment[59], the low expression explaining the persistence of symptoms[60], progression and recurrence rate under treatment[61].

CONCLUSION

Endometriosis affects fertility through multiple mechanisms and in order to effectively treat these patients it is essential to have them in mind. Inflammation may be considered the background, affecting the peritoneal fluid, the ovaries, the follicular fluid, the fallopian tubes and the endometrial cavity, with consequent damages. We may start with the well-known adherence syndrome, with tubal obstruction, peristalsis impairment and defects in oocyte release, pickup or transport. In addition to this, the disorder in follicular function is important, with negative impact upon oocyte quantity and quality, observed by the reduced number of MII oocytes retrieved and lower fertilization rates. The endocrine dysfunction plays another important role, with low follicular growth, affected estrogen and progesterone concentrations, impaired steroidogenesis, disrupted LH surge patterns and low LH concentration in follicular fluid[62]. Reduced fertilization rates by low oocyte quality and quantity, associated with low implantation rates due to altered endometrial receptivity and high uterine contractility complete the picture of infertility related to endometriosis. In addition to this, dysfunctional immune response associated with high pro-inflammatory cells, sperm motility impairment and embryotoxic effect complete the question: why endometriosis patients have fertility problems? This is why fertility preservation should be taken into account in the patients with severe endometriosis[63], best pregnancy rates giving embryo cryopreservation (but with the ethical and legal involvement between the parteners afterwards[64]), next oocytes (that also gives independency to the woman), and ovarian tissue prelevation (that may restore ovarian endocrine function in case of drastical surgery needed).

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