

## Factors Causing Infertility in Women Diagnosed with Endometriosis

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### ABSTRACT

Endometriosis is a pathology that commonly prevails in more than 50% of women as a cause of dysmenorrhea and infertility and we can define it as the presence of endometrial glands and stroma outside of it, that is, ectopic endometrial tissue that is mostly located in the ovaries, Douglas pouch, uterosacral ligaments and other anatomical sites. Infertility associated with endometriosis is a multifactorial disease and there is no certainty about the mechanisms by which it is developed, however there are several theories that could provide an explanation. Oxidative stress is one of the factors that contribute to infertility where a chain of events is created that culminates in the alteration of the number of oocyte recovery and the number of mature oocytes. Dysregulation of aromatase P450 production in steroidogenesis causes a decrease in estrogen production altering follicular and oocyte development. There are also interleukins associated with infertility of which TNF- $\alpha$ , interleukin-1 $\beta$ , IL-6, IL-8, IL-10 and others stand out. On the other hand, there are several biological explanations that are related to the causal link between endometriosis and infertility, some of them include factors of the pelvic cavity, ovarian and genetic factors.

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### INTRODUCTION

Throughout the years and research, the literature mentions that endometriosis is a disease characterized by the development of endometrial tissue, glands and/or stroma outside the uterine cavity, thus forming different types of lesions (peritoneal, deep and cystic ovarian) that induce a chronic inflammatory reaction that leads to pain and infertility, although this may vary in each patient, which is why in this work we are interested in investigating and determining the factors that influence infertility in women with endometriosis<sup>3</sup>.

Different studies have determined that the prevalence of endometriosis in women of reproductive age is 2% to 10%; however, in women with chronic pelvic pain and infertility it can be as high as 50%<sup>2</sup>.

Both endometriosis and infertility are multifactorial, therefore, different mechanisms have been proposed to explain why a disease such as endometriosis may cause infertility<sup>1</sup>.

Current research indicates that the cause of the presence of ectopic tissue is still poorly understood, however, two theories have been put forward that could explain the previous event: one theory is that of endometrial tissue transplantation that diffuses from the endometrium to another location, via the tubal, blood or lymphatic pathways; the second is the metaplastic theory, in which a set of undifferentiated cells present in the organs concerned endometrial-like cells are transformed, these cells have receptors for estrogens, progestogens and androgens, thus responding to exogenous and endogenous hormonal influences that lead to the development of endometriosis itself<sup>5</sup>.

In addition, endometriosis is believed to originate from or be associated with oxidative stress, characterized by an imbalance in the production of species<sup>2</sup>.

Some of the possible biological explanations among the causal link between endometriosis and infertility include pelvic cavity factors (1. chronic inflammatory changes in the

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peritoneal fluid affecting folliculogenesis and luteal function and 2. changes in the peritoneal fluid affecting sperm-oocyte interaction), ovarian factors (1. reduced functional ovarian tissue due to endometriomas, 2. Ovarian dysfunction due to chronic inflammatory changes in the pelvis, 3. Ovaries embedded in adhesions hindering tubo-ovarian contact), uterine factors (1. altered endometrial receptivity due to inflammatory changes, 2. autocrine estrogen production and progesterone resistance and 3. myometrial dysperistalsis causing altered uterotubal transport) and genetic factors<sup>1</sup>.

The pain often experienced by patients with endometriosis, particularly dyspareunia, can lead to a reduction in the frequency of coitus and thus influence the chances of natural conception<sup>1</sup>.

This research was conducted with the objective of determining the factors that influence infertility in women diagnosed with endometriosis.

Endometriosis is the presence of glands and endometrial stroma outside the endometrium, it is considered ectopic tissue, and the most frequent places where it occurs are: ovaries, Douglas' cul-de-sac, uterosacral ligaments, uterine body, rectovaginal septum, vagina, cervix, although it can occur in any part of the body (11).

Not much is known regarding the mechanisms of infertility in endometriosis; however, a variety of factors such as anatomic failures, pelvic adhesions, and inflammatory cytokines have been implicated. "The cause of this enigmatic disease is unknown, however, the theory of retrograde menstruation is widely accepted. This theory suggests that endometrial tissue shed during menstruation is thrown into the fallopian tubes and the peritoneal cavity during uterine contractions generated during menstruation" (5).

Women who develop endometriosis should be considered to have a dysfunction, which can vary between genetic, biochemical or immunological. It has been confirmed that these patients have an alteration of the immune system. There are irregularities in the expression of immune cells, as well as in the expression of the immune system. endometrial tissue and peritoneal fluid of patients with endometriosis, there is an increased presence of cytokines and chemokines that are released during inflammation, angiogenesis and growth factors (12).

### OXIDATIVE STRESS AS A CONTRIBUTING FACTOR TO INFERTILITY IN ENDOMETRIOSIS

The mechanism is not entirely clear, however there is evidence that oxidative damage compromises the follicles decreasing fertility. Excess reactive oxygen species in granulosa cells in women with endometriosis activate endoplasmic reticulum stress and create senescence that impairs mitochondrial function, likewise  $\beta$ -galactosidase-associated senescence activity, soluble advanced glycation end product receptor isoform expression, follicular fluid and senescence-associated secretory phenotype factors is

significantly related to the number of oocyte retrieval and number of mature oocytes in patients with endometriosis. It was recently reported that the increased ratio of age and soluble receptor isoform of advanced glycation end products in follicular fluid was associated with activation of the unfolded protein response in granulosa cells and led to decreased competence in oocyte development.

As a consequence, this has left a question that leads us to investigate even further the real etiology of infertility in mild grades (I), reflected in only 22.1%<sup>(4)</sup> of the total number of women who achieve pregnancy even at this early stage of the disease.

In the particular situation of endometriosis located in the pelvis, it has been known that oxidative stress promotes lipid peroxidation, which generates substances that end up activating the creation of antibodies, since they are detected as a foreign body for the organism. Consequently, erythrocytes and endothelial cells are affected, and then through chemotaxis, recruit macrophages that will continue to cause chronic inflammation.

### DYSREGULATION OF STEROIDOGENESIS

Dysregulation of aromatase P450 production in steroidogenesis has been shown to cause a decrease in estrogen production. This results in lower concentrations of E<sub>2</sub> during the preovulatory phase, which is necessary for follicular and oocyte development, and in the emergence of luteinizing hormone.

In studies that have been carried out for assisted reproduction techniques, evidence was shown of postovulatory alterations, where there is an abnormal secretion of progesterone that affects oocyte maturation.

### DISRUPTION OF THE INTRAFOLLICULAR ENVIRONMENT

In recent years, studies have been published on the affection of follicular fluid, decreased E<sub>2</sub> and increased progesterone. This influences steroidogenesis and the oocyte environment. Oxidative stress together with reactive oxygen species promote meiotic abnormalities and chromosomal instability, causing a reduction in the quality of the exposed oocyte. Normally the oocyte would stop in prophase I and through the meiotic spindle would have cytoplasmic and nuclear maturation; however when there is oxidative stress in the follicular fluid these microtubules are compromised.

One indicator of oxidative DNA damage is 8-hydroxy-2'-deoxyguanosine, which is often found to be elevated in women with endometriosis. Other data that are still being studied but have been related to oxidative stress and infertility are: polymorphisms in brain-derived neurotrophic factor or BDNF and oral supplementation with vitamin C and E in severe endometriosis undergoing in vitro fertilization treatment; the latter appears to cause a significant decrease in myeloperoxidase in follicular fluid. (7)

The environment of the oocyte damaged by inflammation has

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been extensively studied. It has been suggested that the cytokines present in the follicular fluid modulate folliculogenesis, so that their alteration affects oocyte development. In fact, in the follicular aspiration of these patients, specifically, increased concentrations of IL-8 and IL-12 were found, resulting in poor oocyte maturation and quality. In addition, the presence of proinflammatory interleukins in peritoneal fluid have been implicated as direct oocyte meiotic spindle disruptors.

### INTERLEUKINS IN ENDOMETRIOSIS ASSOCIATED WITH INFERTILITY

Elevated levels of TNF- $\alpha$ , interleukin-1 $\beta$ , IL-6, IL-8, IL-10, IL-13, IL-17, IL-33, MCP 1, MIF, and RANTES are associated in patients with endometriosis and infertility. Due to the presence of these molecules, inflammation is created, but what leads to damage is the chronicity of this state. This is how it results in a local hormonal imbalance that will have the consequence of providing a bad environment for the oocyte, the spermatozoon, and to a certain degree, the embryo. Specifically, several qualities are damaged in the sperm that make it less capable of carrying out fertilization, such as reduced motility, abnormal acrosomal reaction, and ultimately the fusion of the sperm with the oocyte.

### ENDOMETRIOSIS AND INFERTILITY: INSIGHTS INTO THE CAUSAL LINK AND MANAGEMENT STRATEGIES.

Infertility related to endometriosis or in women diagnosed with endometriosis is associated with pelvic inflammation, systemic immunological changes and endometrial changes<sup>1</sup>. There are several biological explanations that relate to the causal link between endometriosis and infertility, some of which include pelvic cavity factors, ovarian factors, uterine factors and genetic factors<sup>1</sup>.

**Pelvic cavity factors:** inflammatory changes in the peritoneal fluid that affect folliculogenesis and luteal function; changes in the peritoneal fluid that affect sperm-oocyte interaction; mechanical defects such as distortion of the fallopian tube anatomy that hinder ovarian tube contact<sup>1</sup>.

**Ovarian factors:** reduced functional ovarian tissue due to endometriomas and/or surgery; ovarian dysfunction due to chronic inflammatory changes in the pelvis; and mechanical factors such as ovaries embedded in adhesions that hinder ovarian tube contact<sup>1</sup>.

**Uterine factors:** altered endometrial receptivity due to chronic inflammatory changes; autocrine estrogen production and resistance to progesterone and myometrial dysperistalsia causing altered uterotubal transport<sup>1</sup>.

In addition to all these factors, pain, in particular dyspareunia, can lead to a reduction in the frequency of coitus and therefore, this can decrease the chances of natural conception<sup>1</sup>.

### OXIDATIVE STRESS AS A POSSIBLE MECHANISM UNDERLYING THE PATHOGENESIS OF MILD ENDOMETRIOSIS-RELATED INFERTILITY

In relation to the laparoscopic findings, endometriosis can be classified according to its severity as: minimal (stage I), medium (stage II), moderate (stage III) and severe (stage IV). Fertility is usually affected in women with endometriosis from the early stages (stage I and II) of the disease<sup>2</sup>.

Endometriosis is thought to be related to oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and their neutralization by the antioxidant system<sup>2</sup>.

Oxidative stress is considered a process involving three distinct phases: 1) increased production of ROS, 2) mobilization of enzymatic and non-enzymatic antioxidants to neutralize oxidative damage, and 3) oxidative damage to proteins, lipids, DNA and other molecules<sup>2</sup>.

In the pilot study carried out in this article, patients with infertility associated exclusively with stages I and II endometriosis were chosen, patients diagnosed and classified through laparoscopy according to the criteria of the American Society For Reproductive Medicine (ASRM) and a control group of patients with male factor infertility<sup>2</sup>.

Low ROS concentrations were found to be important for the modulation of oocyte maturation, follicular atresia, corpus luteum function, gamete interaction, fertilization and embryo implantation and development, however, it was found that supra-physiological levels of ROS can impair these processes, as increased ROS and consequently oxidative stress can disrupt the early follicular phase of the menstrual cycle and this leads to higher rates of infertility in women diagnosed with endometriosis<sup>2</sup>.

### MORPHOLOGICAL CHANGES

Oocyte morphological changes have been little studied mainly because of the need for invasive techniques, however, it is considered that they could be very useful as predictors of clinical outcome. Cytoplasmic granularity, presence of vacuoles or factors causing the morphological changes, e.g. ovarian stimulation and hormonal environment, have been widely discussed (8).

Physicians who have conducted studies on this subject have concluded that oocytes in endometriosis have increased loss of cortical granules and hardening of the zona pellucida. Evidence of dimorphism, increased extra-cytoplasmic incidence and defective oocytes has also been demonstrated in endometriosis.

### DISCUSSION

As we have seen, endometriosis is a disease whose true etiopathogenesis is still unknown, however, several theories have been established to explain it, where Sampson's theory, that retrograde menstruation spreads endometrial tissue expelled by uterine contractions to other pelvic organs, is the most accepted to date.

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Based on the literature researched, it is mentioned that the incidence of infertility in women diagnosed with endometriosis is 25-50%, i.e. it can increase the possibility of being infertile twice as much, unlike a woman not diagnosed with endometriosis. This is the question that led us to conduct this research, what is the relationship between endometriosis and the development of infertility in women who suffer from it. The results show that there are different pathophysiological factors, the most important of which are: activation of the immune response, oxidative stress, dysregulation of steroidogenesis and disruption of the follicular environment.

We can explain all this as a domino effect, everything starts from the presence of something abnormal in the body, that is, the ectopic endometrial tissue that is formed by endometriosis, causes an alert by the immune system, as it recognizes it as external to it, and assumes it harmful, this progresses to an activation of the immune response, generating an inflammatory process (here is the immune factor), where several important cytokines and free radicals that are toxic will be released, these cause severe damage to the tissue of the organ affected by endometriosis, in if acute inflammation is not what damages, if not the chronicity of this process, that every time there is a menstrual cycle is activated again. This is followed by the development of scar tissue or adhesions in the affected organs, causing alterations in their functioning. Focusing on infertility, and in that the ovary is one of the most frequent sites where endometriosis can be found, when the ovarian tissue is damaged, it can generate alteration of steroidogenesis, estrogen or progesterone, not having these hormones that are vital for ovulation and pregnancy, the patient can be infertile, and also in a physical way to be surrounded by adhesions, the egg in its early stages may not mature due to alterations in the intrafollicular environment, and if it is generated (graafian follicle) there may be difficulty in transporting it to the isthmus where the sperm would be ready to fertilize it (if the patient was trying to get pregnant) or conversely the sperm could not reach the site of fertilization, due to the presence of adhesions or tissue damage in the fallopian tubes.

After the investigation this was the result we obtained, endometriosis generates a domino effect, the later it is diagnosed and treated, the greater the consequences up to infertility. Currently we can see in women of childbearing age and even in adolescents, that although they have menstrual cramps so painful that they disable their daily activities or generate symptoms such as nausea, vomiting, headache, they take it as something normal, and only take painkillers to try to reduce it instead of treating it with a gynecologist specialist. It is very important that any patient who has very painful and disabling menstrual cramps, heavy bleeding, dyspareunia or pain when defecating, between the days before or after their period should visit the gynecologist.

### CONCLUSION

The percentage of women with endometriosis associated with

infertility is really high, both being the main reasons for gynecological consultation when pregnancy is desired. Fertility is affected through multiple pathways where the pathogenesis remains unclear, but of all these, oxidative stress is the most significant as it is the culprit of meiotic and infertility abnormalities.

chromosomal instability affecting the quality of the oocyte, as well as hormonal imbalance, which affects the environment where the oocyte develops. It is important to study in depth and as a whole all the factors related to infertility in endometriosis, to carry out clinical trials and to propose therapeutic options so that according to the analysis and condition of each patient, an adequate option can be given so that the patient can become pregnant. Above all, as physicians, the infertile woman's experience must be taken into account, since it has a significant psychological impact that affects her well-being, giving rise to low self-esteem, anguish, depression, guilt, frustration and problems within the couple's relationship.

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