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Implementation of Dienogest as a Treatment for Infertility in Women with Endometriosis

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ABSTRACT

Fertility problems affect between 4 and 5 million couples each year in Mexico alone, according to data recorded by the National Institute of Statistics and Geography (INEGI). Endometriosis is a benign disorder characterized by the presence of endometrial tissue outside the uterine cavity, which are estrogen-dependent and have resistance to progesterone. The main clinical manifestations are pelvic pain, infertility and the presence of an adnexal mass. The use of transvaginal ultrasound is able to detect endometriomas >20 mm. The gold standard is diagnostic laparoscopy. One of the drugs that has begun to be used in the management of infertility in patients who are candidates for in vitro fertilization is Dienogest,which is a fourth generation progesterone agonist. Dienogest has been shown to be effective in most cases and shows potential for treating and resolving infertility associated with endometriosis and added symptoms.

.**KEYWORDS:** Infertlity, endometriosis, Dienogest, Obstetrics, female

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INTRODUCTION

Fertility problems are one of the most common worldwide, affecting between 4 and 5 million couples each year in Mexico alone, according to data recorded by the National Institute of Statistics and Geography (INEGI)[1], having a significant impact on the quality of life, both physically and emotionally.

Endometriosis is one of the main causes of female infertility, according to the World Health Organization (WHO), with an estimated prevalence of 176 million[2]. It affects young women in the reproductive stage, with an average age of presentation of 27 years and a maximum prevalence between 35 and 45 years[3] of age.

Women with endometriosis-associated infertility often require assisted gestational technology, such as in vitro fertilization and embryo transfer, to achieve pregnancy; however, the success rate is lower than in women without endometriosis[4].

Due to the above, the present documentary research is justified, in order to identify in a timely manner this condition, and explore an optimal therapy in patients who wish to conceive, comparing the current therapeutics of clinical practice guidelines and books, withdrugs that are Beginning to be used in the treatment of the disease.

THEORETHICAL FRAMEWORK

Endometriosis is defined as a benign disorder characterized by the presence of functional endometrial tissue, glands and stroma outside the uterine cavity, mainly in the ovaries and on the surface of the pelvic peritoneum, which induces a chronic[5, 6] inflammatory reaction. The most frequent sites of involvement are the ovaries, Dougas pouch, uterosacral ligaments, posterior aspect of the broad ligament, rectovaginal septum and pelvic[7] peritoneum.

Likewise, different studies show that the left pelvis is more susceptible[6]. As for extrapelvic endometriosis, the most frequent sites are the sigmoid rectum, bowel, ureters and bladder[6].

Historical background.

The first reference to this disease appears in 1690, when the German physician Daniel Shroen described the presence of "ulcers" spread throughout the abdomen, especially in the lower pelvis, which appeared only in women of Reproductive8 age.

Etiopathogenesis.

The definitive mechanism by which this condition occurs is unknown; however, several theories have been proposed to support the pathophysiology of the disease:

-Retrograde menstruation is the most accepted and proposes that endometriosis is secondary to a retrograde flow of menstrual contents through the fallopian tubes, with subsequent dissemination into the peritoneal cavity. It also supports the concept of uterine hyperperistalsis and dyserysalsis which causes a greater endometrial[6] reflux.

-Lymphatic or vascular dissemination of endometrial tissue, which suggests that dissemination occurs from the lymphatic vessels to the sentinel nodes in the pelvis, explaining the abnormal locations, such as the perineum or the inguinal[6] region.

-The presence of stem cells or indifferent endometrial cells in the basal layer of the endometrium determines that these cells differentiate into epithelial, stromal and vascular cells. When these cells move to an ectopic site and subsequent maturation occurs, endometriosis[6] develops.

-The induction theory states the existence of hormonal or biological factors that condition thedifferentiation of cells to generate endometrial tissue. The hormonal factors considered to be the most important in this theory are estrogens[6].

-Embryonic remnants theory, which explains the persistence of remnants of Müllerian ducts,in their embryonic migration, which causes abnormal differentiation, predisposing to the formation of endometrial tissue in extrauterine[6] regions.

Molecular mechanisms

Endometriotic implants are estrogen-dependent and show resistance to progesterone. This is supported by the identification of expression of aromatase and 17β-hydroxysteroid dehydrogenase type 1 by the endometriotic tissue, which are responsible for the conversion of androstenedione into estrone and estradiol. Likewise, resistance to progesterone is observed due to a low concentration of receptors for this hormone inside the implants[6].

On the other hand, prostaglandin E2 acts as an inducer of aromatase activity in endometrial stromal cells. Estradiol produced by aromatase enhances prostaglandin production by stimulation of cyclooxygenase-2 (COX-2) in uterine endothelial cells, promoting a positive feedback loop and enhancing estrogenic effects on endometriosis[6] proliferation.

Risk Factors

The factors whose presence increases the risk of endometriosis are the following:

Dysmenorrhea, menstrual alterations of which hypermenorrhea and proiomenorrhea (cycles lasting <21 days), early menarche (<11 years), structural alterations such as imperforate hymen or cervical atresia, which prevent normal menstrual flow and cause retrograde menstrual flow[6].

Protective factors

There are antecedents in patients that decrease or even prevent the development of endometriosis. Most of these involve decreasing estrogen levels, thus preventing thickening of the endometrial wall. These include multiparity and lactation, BMI <30 kg/m2, use of oral contraceptives, and any other estrogen-lowering alterations such as smoking and exercise[6].

Clinical picture

The main clinical manifestations of endometriosis are composed of a characteristic triad: chronic pelvic pain, cramping, stabbing in the hypogastrium, and radiating to the back and legs; infertility; and the presence of an adnexal mass. Chronic pelvic pain is a non-cyclic pain, secondary to proinflammatory cytokines and prostaglandins released by endometriotic implants that lasts more than 6 months. Dyschezia (pain with defecation), dysuria, lumbago and abdominal[3,6] pain may be present.

Some women describe dysmenorrhea 24 to 48 hours before menstrual flow, persisting throughout menstruation[7]; as well as dyspareunia, which arises from the rectovaginal septum, uterosacral ligament and posterior cul-de-sac, which is accentuated in the perimenstrual[7] period.

The presence of ovarian endometriomas has been described, which consist of ovarian cysts with uniform walls, dark brown in color, filled with a chocolate-like liquid and may be uniloculated or multiloculated[3].

Most women usually come for consultation due to difficulty in getting pregnant, which may be due to infertility secondary to the presence of adhesions or fibrosis in the tuboovarian[7] region, which hinder the normal uptake of the oocyte and its transport through the fallopian tube. In stage III and IV endometriosis, tubal and ovarian deformation may occur, causing adecrease in fertility.

When there is extrapelvic endometrial tissue, patients may present with suprapubic pain, pollakiuria, urgency and hematuria if there is genitourinary tract involvement; cyclic chest orshoulder pain, hemoptysis or hemothorax when there is thoracic involvement, among others[7].

Diagnosis

Early lesions are small (2 to 5 mm), vesicular, pink or red (flaming) that with the passage of time become darker (powdery grain lesions) acquiring a blue-grayish color in the neck or posterior vaginal fornix with inflammation and infiltration of adjacent structures causing typically stellate scars and nodules of variable size. These lesions may be painful to the touchor bleed[7].

On bimanual palpation, anatomical abnormalities suggestive of endometriosis are identified, such as nodules and pain on touch of the uterosacral ligament, a cystic mass in the adnexa representing the ovarian endometrioma, which may be mobile or attached to other pelvic structures, the uterus

may be painful, fixed, in retroversion and the posterior fundus sac fixedand firm[7].

Laboratory studies may include blood biometry to rule out infections; measurement of the β- hCG fraction to assess gravid complications. When endometriosis of the urinary tract is suspected, renal function is assessed with creatinine[6] concentrations.

Likewise, the measurement of CA 125 levels can be useful in cases of a high suspicion of endometriosis, however, this serum marker is not used to make the diagnosis because it can be found elevated in other pathologies (6). Values above 35 IU/ml between the first and third day of the menstrual cycle lead to a diagnostic suspicion of endometriosis[3,6].

Among the imaging studies, transvaginal ultrasound is recommended as a first step forpatients with a diagnosis of endometriosis and clinical suspicion of the presence of endometriomas. This study is capable of detecting endometriomas >20 mm, which are observed as low-level, homogeneous echoes, with ground-glass[3,6] echogenicity.

Once the transvaginal USG has been performed and if resources are available, the use of computed tomography (CT) is recommended for the detection of endometriomas in the abdominal wall, bowel and ureters. In addition to this study, magnetic resonance imaging

(MRI) is also recommended as it is the most sensitive study for the detection ofendometriomas[6].

The gold standard for diagnosis is diagnostic[3,7] laparoscopy. Circumscribed endometriotic lesions, endometriomas or adhesions can be observed. These may be red, white or black. The implants are usually located in the serosa of the pelvic organs and in the pelvic[3] peritoneum.

On the other hand, clinical practice guidelines recommend performing a biopsy at diagnostic laparoscopy. In the histological report, the finding of two or more of the following establishesthe definitive diagnosis:

-Endometrial epithelium
-Endometrial glands
-Endometrial stroma
-Macrophages with hemosiderin

Considering the above, the absence of these in the biopsy does not rule out the presence ofendometriosis.

It is important to mention that in the presence of endometriomas > 4 cm and deep endometrial lesions, it is mandatory to perform a biopsy to rule out the presence of malignantlesions that predispose to endometrial[6] cancer.

Dienogest (17-hydroxy-3-oxo-19-nor -17alpha-pregna-4,9-dien-21-nitrile) is a fourth generation progesterone agonist[10], which has several properties. Among these are high affinity for progesterone receptors and low affinity for estrogenic, androgenic, glucocorticoidand mineralocorticoid receptors, thus giving it antagonistic properties to these hormones. As previously mentioned, it has been noted that dienogest has progestagenic and antiestrogenic properties in eutopic and ectopic endometrial tissue, decreasing the hormonal levels mentioned in these tissues[9].

This progestin has several mechanisms of action. In the first instance, it inhibits the enzyme aromatase and 17β-hydroxysteroid dehydrogenase type 1 in stromal cells of endometriomas. In addition, it increases endometriotic cell apoptosis and decreases the production of interleukin 8[4,9], a proinflammatory cytokine released by endometrial stromal cells; it also decreases the production and release of angiogenic factors stimulated by estradiol such as vascular endothelial growth factor and stromal[9] cell-derived factor.

After ingestion, dienogest has 91% bioavailability: 10% of the serum concentration of the drug is available as a free steroid and the remaining 90% is bound to albumin. It is metabolized in the liver by the CYP3A4 enzyme complex and its resulting products are excreted in the urine and feces[9,10].

Contraindications for the use of this drug include cardiovascular and thromboembolic conditions, history of liver disease, sex hormone-dependent malignancies and undiagnosed[9,10]abnormal transvaginal bleeding.

DISCUSSION

Endometriosis and infertility are closely related. However, the association of the two has notbeen clearly explained. A study in Australia reported that metalloproteinases influence inadequate implantation and proinflammatory cytokines have an effect on inadequate embryo[11] development.

Pritts, et al., agrees with the above, emphasizing that one of the main mechanisms of endometriosis that induce infertility in women is an aberrant activation of inflammatory and immune responses that drastically alter fertility in women, such as monocytes and natural killer[12] T-lymphocytes.

Therefore, treatments are sought for this condition resulting from endometriosis, which have a mechanism that goes against the potent inflammatory response that induces infertility, this mechanism being one of the main characteristics of dienogest[13] .

The efficacy of Dienogest has been the subject of controversy in several studies, whose objectives were to corroborate the existence of any advantage in the use of the drug prior to the performance of in vitro fertilization (IVF), or on the contrary, the lack of concrete data on any fertility support in women with endometriosis; agreeing with several studies that these failures are associated with a decreased ovarian reserve, altered endometrial receptivity and low embryo[14] quality.

In a retrospective study, which included 151 women, Dienogest was observed to have a beneficial effect on systemic and intralesional inflammatory microenvironments in patientswith endometriosis by decreasing the secretion of IL-8, IL-6 and monocyte chemotactic protein 1, as well as TNF-α-stimulated mRNA production in endometrial stromal cells

Isolated from affected patients, thus providing that IVF outcomes can be improved by pretreatment with dienogest[15] . These results are in agreement with several studies, such as the one by Grandi, et al. where endometrial stromal cells, from women diagnosed with endometriosis and infertility, were cultured with TNF-α to stimulate an inflammatory response. Subsequently, these were treated with Dienogest, finding a suppression of proliferation of inflammation stimulated by TNF-α, which interrupted the subsequent secretion cycle of proinflammatory cytokines such as IL-6, 8 and monocyte chemotactic protein, providing a favorable environment for IVF[13].

Similarly, in a prospective cohort study conducted by Muller, et al. which included 144 infertile women of reproductive age (23-42 years), who were going to undergo IVF after laparoscopic resection of ovarian endometriomas, were divided into three groups, of which the first group was administered 2 mg of dienogest daily for 6 months prior to IVF, in the second group they received six injections of triptorelin 3.75 mg every 28 days pre-cycle and finally in group three no hormonal treatment was administered. It was inferred that the greatest effect was presented in the women who received dienogest, this effect being a greater incidence of pregnancy, which was defined as the presence of the fetal focus in a transvaginal ultrasound at 6-7 weeks of gestation. Therefore, it is established that dienogest is an effective alternative for infertility due to the absence of antigonadotrophic effects and ovarian suppression, as well as its beneficial effect in improving the results of IVF: clinical pregnancy and live[14] birth rates.

In contrast, Tamura et al, in their prospective outpatient investigation at the Yoshida Ladies' Clinic and Saiseikai Shimonosek[4] General Hospital, contradicted Barra, Muller, Grandi et al, stating that treatment with Dienogest prior to in vitro fertilization with embryo transfer in infertile women with endometriosis reduced the number of growing follicles, retrieved oocytes, fertilized oocytes and blastocysts, thus resulting in a reduction in gestational[4] contribution.

Being a topic of discussion, recapitulating that, some time lapse between dienogest therapy and ovarian stimulation is necessary to allow small follicles to become antral follicles, capable of arguing to FSH stimulation, resulting in an increase in the number of developing follicles[4].

Comorbidities associated with Dienogest use have been little studied, although a 2017 retrospective study found that there are five factors related to treatment response and they are, primary dysmenorrhea, suspected adenomyosis, duration of treatment, genital bleeding during treatment, and rASRM[16] stage .

According to the study by Nirgianakis et. al. of women discontinuing treatment in response to side effects, the most frequently mentioned were due to bleeding disorders, mood disorders, weight gain, decreased libido, acne, headache, gastrointestinal discomfort, hair loss and thrombophlebitis[16] .

In addition, a systematic review by Becker et al[17] . concluded that 11% - 19% and 5% - 59% of patients with endometriosis who were treated with hormone therapy had no pain reduction or had remaining pain, respectively. In addition, 15.6% - 26.1% and 10% - 43.5% of patients discontinued therapy due to ineffectiveness or side effects, respectively. These data are in agreement with the results of the study by Konstantinos et. al in both patients with nonresponse and for those who discontinued Dienogest.

CONCLUSION

It is concluded that the use of Dienogest as a treatment for endometriosis was effective in most cases and it is shown as a progestin with potential to treat and resolve infertility associated with endometriosis as well as its added symptoms.

Regardless of the analyses and conclusions made in this review, its usefulness in treating infertility cannot be fully affirmed since it is a drug that is still under study for that use.

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