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The effect of hormones on endometriosis development

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Endometriosis is a common gynecological condition in which tissue that is histologically similar to the endometrium with glands and/or stroma grows outside the uterine cavity and can lead to pelvic pain, dysmenorrhea and infertility. Many aspects of female reproductive function are strongly influenced by genetic factors and numerous studies have attempted to identify susceptibility genes for disorders affecting female fertility such as endometriosis. The importance of steroid hormones on endometriosis is unquestionable. The disease is most prevalent in women of reproductive age and regresses after menopause and its occurrence before menarche has not been reported. Sex steroids, estrogen and progesterone, are mainly produced in the ovaries and they regulate the growth of endometrial tissue, basically by stimulating and inhibiting cell proliferation, respectively. In addition, estrogen plays an important role in the regulation of cyclic gonadotropin release and in folliculogenesis. Numerous studies have been conducted to demonstrate the interaction of hormone and their receptors with endometriosis with conflict results. Besides, environmental chemicals, known as endocrine disruptors, have the capacity to mimic, block or modulate the endocrine system through the interaction with steroidal receptors. Recently evidences have proposed a putative role for ubiquitous environmental contaminants in the occurrence of endometriosis. Here, we reviewed significant articles regarding the interaction among endometriosis, hormones and genetic polymorphic variants.

Key words: **Endometriosis - Infertility - Estrogens - Progesterone - Luteinizing hormone.**

Endometriosis is a common gynecological condition in which tissue that is histologically similar to the endometrium with glands and/or stroma grows outside the uterine cavity and becomes implanted in tissues and organs such as the Fallopian tubes, ovaries, peritoneum, colon, the retovaginal region and the bladder, leading to a chronic inflammatory process.[1] The presence of this ectopic tissue can cause pelvic pain, dysmenorrhea and infertility [2, 3] but the symptoms are not correlated to the disease severity. However, it is currently estimated that 25% to 50% of women with endometriosis are infertile and that 25% to 30% of all infertile women have endometriotic lesions as the only identifiable cause for infertility.[2-5] It was noted that endometriosis can also be found in 16% of fertile women.[5]

Conflicts of interest.—None.

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TABLE I.—*A summary of candidate genes from genetic association studies with endometriosis.*

Gene	Chromosome	SNP	Association	No association
ESR1	6q25	*Pvu*II (T-397C/rs2234693)	Luisi *et al.* (2006) [28]	Wang *et al.* (2004) [15]
		*Xba*I (A-351G/rs9340799)	-	Wang *et al.* (2004) [15] Luisi *et al.* (2006) [28]
ESR2	14q23-24	*Rsa*I (G1082A/rs1256049)	-	Wang *et al.* (2004) [15]
		*Alu*I (G+1730A/rs4986938)	Wang *et al.* (2004) [15] Bianco *et al.* (2009) [30] Zulli *et al.* (2010) [31]	Luisi *et al.* (2006) [28] Lee *et al.* (2007) [29]
COMT	22q11.2	Val/Met (G472A/rs4680)	-	Wieser *et al.* (2002) [33] Juo *et al.* (2006) [34] Christofolini *et al.* (2011) [35]
CYP17A1	10q24.3	MspA1 (T-34C/rs743572)	Hsieh *et al.* (2004) [39] Bozdag *et al.* (2010) [40]	Kado *et al.* (2002) [36] Asghar *et al.* (2005) [41] Huber *et al.* (2005) [46] de Carvalho *et al.* (2007) [43] Vietri *et al.* (2009) [44]
CYP19	15q21.1	Trp39Arg (T115C/rs2236722)	Yang *et al.* (2010) [13]	-
		TTTA VNTR	Arvanitis *et al.* (2003) [45]	-
		Arg264Cys (C790T/rs700519)	-	Huber *et al.* (2005) [42] Tsuchiya *et al.* (2005) [4]
		*19C/T(C1558T/rs10046)	Kado *et al.* (2002) [36] Vietri *et al.* (2009) [44]	Huber *et al.* (2005) [42]
HSD17	17q11-q21	vIV A/C	Huber *et al.* (2005) [42]	-
		Gly313Ser(G937A/rs605059)	Tsuchiya *et al.* (2005) [4] Lamp *et al.* (2010) [16]	-
PR	11q22-23	PROGINS (ins Alu/ rs1042838)	Wieser *et al.* (2002) [51] Lattuada *et al.* (2004) [52] De Carvalho *et al.* (2007) [43] D´Amora *et al.* (2009) [55]	Govidan *et al.* (2007) [53] van Kaam *et al.* (2007) [54] Gimenes *et al.* (2010) [56] Near *et al.* (2011) [57]
LH	19q13.3	G1502A (rs5030774),	Liao *et al.* (1998) [67] Mafra *et al.* (2010) [68]	Kim *et al.* (2001) [69] Gazvani *et al.* (2002) [70]

Many aspects of female reproductive function are strongly influenced by genetic factors and numerous studies have attempted to identify susceptibility genes for disorders affecting female fertility.[1, 3, 6] Studies of the genetic bases of endometriosis suggested that it is a polygenic/multifactorial disease, associated with a complex interaction of hormones and cytokine activation, immune-inflammatory processes and genetic factors.[7] The genetic influence on endometriosis is also demonstrated by the familial recurrence of disease in first-degree of female relatives of affected women and by evidence on monozygotic twins.[8-10]

The importance of steroid hormones on endometriosis is unquestionable. The disease is most prevalent in women of reproductive age and regresses after menopause and its occurrence before menarche has not been reported.[11] Estrogen is necessary for proliferation of the uterine epithelium [2, 12] and inhibited by progesterone.[13, 14] In fact, most current endometriosis treatment blocks either estrogen production or its action.[15]

Sex steroids, estrogen and progesterone, are mainly produced in the ovaries and they regulate the growth of endometrial tissue, basically by stimulating and inhibiting cell proliferation, respectively. In addition, estrogen plays an important role in the regulation of cyclic gonadotropin release and in folliculogenesis.[15, 16]

Numerous studies have been conducted to demonstrate the interaction of hormone and their receptors with endometriosis and their rationale will be discussed in details in the next topics (Table I).[17-70]

Estrogen

The physiological response of estrogen on diverse tissue and organ occurs by the hormone binding to estrogen receptor (ER), which is a nuclear receptor protein.[14] There are two specific receptors, estrogen receptor α (*ERα*) encoded by the *ESR1* gene (MIM 133430/Genbank ID 2099) on chromosome 6q25 [17] and estrogen receptor β (*ERβ*) encoded by the *ESR2* gene (MIM 601663/Genbank ID 2100) on chromosome 14q23-24.[18]

Using a variety of laboratory methods, several investigators have demonstrated that ectopic endometriotic implants contain both estrogen receptors.[19, 20] Estrogen receptor α displays a higher affinity for estrogen and is the predominant form in normal endometrium. Because large amounts of *ERβ* messenger ribonucleic acid (mRNA) are found in ovaries and granulosa cells, *ERβ* is likely to play a role in the ovulatory function.[21] Previous studies have demonstrated that both *ERα* and *ERβ* are expressed in human endometriotic tissues,[22] but the distribution of the isoforms is different between eutopic endometrium and ovarian endometriotic tissues.[23]

Estrogen has showed to have a large influence on endometriosis. It was observed that ectopic endometrium expresses persistent estrogen receptors with hormonal independence during the luteal phase.[24] Takahashi *et al.* (1989) [25] measured estradiol levels in peripheral and menstrual blood of patients with endometriosis, adenomiosis and controls. They found no difference in estradiol levels in peripheral blood. However, menstrual blood showed highest levels in patients with adenomiosis, followed by patients with endometriosis than in controls, suggesting a uterine production of estrogen in these diseases. In addition, endometriotic implants have been shown to express aromatase, principally cytochrome P450, an enzyme that catalyzes the conversion of androgens to estrogens, suggesting that local estrogens production can increase estrogen concentration and together with circulating estrogen can stimulate the growth of endometriotic lesions.[11] The presence of aromatase also allows the maintenance of endometriotic lesions on a low estrogen microenvironment.

Matsuzaki *et al.* (2001)[26] demonstrated that cyclical changes in ovarian hormones have different effects on *ERα* and *ERβ* mRNA expression in normal and endometriotic tissues. They showed that the expression of *ERα* was more predominant than that of *ERβ* in eutopic endometrium and ovarian endometriotic tissue, suggesting that the principal and regulatory effects of estrogen are mediated mainly via *ERα* rather than *ERβ* in both control and endometriotic tissues. In contrast, Fazleabas *et al.* (2002) [27] examined the expressions of *ERα, ERβ,* and progesterone receptors (*PR*) in baboons by using immune-cytochemical analyses, and their results revealed that *ERβ* was the dominant steroid receptor present in endometriotic explants, regardless of the cycle phase. They also demonstrated that *ERα* and PR were present at lower levels than in eutopic endometrium from the same animal.

Several variants in ER genes have been described, principally *PvuII* (T-397C/rs2234693) and *XbaI* (A-351G/rs9340799) polymorphisms in the *ERα* gene and *AluI* (G+1730 /A/rs4986938) and *RsaI* (G1082A/rs1256049) polymorphisms in the *ERβ* gene and authors have been searching for their contribution for endometriosis development with conflicting results.

Wang *et al.* (2004) [15] studied 132 Japanese women with endometriosis and 182 controls by RFLP-PCR for *AluI* and *RsaI* polymorphisms in the *ERβ* gene and for *PvuII* and *XbaI* polymorphisms in the *ERα* gene and found that the *AluI* polymorphism was associated with an increased risk of stage IV endometriosis. Luisi *et al.* (2006) [28] studied *ERα* (*PvuII* and *XbaI*) and *ERα* (*AluI*) in 61 women with endometriosis and found a statistically significant correlation between *PvuII* polymorphism and the recurrence of endometriosis. Lee *et al.* (2007) [29] studied 239 Korean women with endometriosis and 283 controls and found no association between *AluI* polymorphism and endometriosis. Our research group [30, 31] found association between *AluI* polymorphism and

endometriosis and endometriosis associated infertility.

Polymorphisms in genes related to estrogen metabolism have also been studied as *COMT* (G472A, rs4680, val158met), cytochrome P450 - *CYP*17A1 (MspA1, T-34C/rs743572), *CYP*19 Arg264Cys (C790T, rs700519, Gly313Ser), *CYP*19 (T115C, rs2236722, Trp39Arg), associated to changes in serum estrogen concentrations, *HSD*17 (v1V - A/C) that participates on conversion of estrone to E2. All these polymorphisms studies also showed conflicting results.

COMT enzyme is a crucial element in estrogen metabolism and the polymorphism val158met, which changes enzyme activity, was suggested to be involved in the development of endometriosis.[32] However, Wieser *et al.* (2002) [33] found no differences of allelic distribution of *COMT* val158met polymorphism in an Austric population. Juo *et al.* (2006) [34] also found no association of *COMT, CYP1A1* or *CYP*17 polymorphisms with endometriosis in a Taiwanese population. Our group,[35] in a study of Brazilian infertile women with endometriosis found no difference on allele distribution of *COMT* polymorphism.

CYP17A1 gene, located at 10q24.3, codifies the P450c 17α enzyme, that participates on the 17α hidroxilase, and 17-20 lyase activities and plays a key role in androgen biosynthesis.[36] The 5'untranslated region of *CYP*17 contains a polymorphism (MspA1, T-34C, rs743572) that creates an additional promoter site on the gene.[37] It was observed inherited levels of estrogens in patients carrying the mutated allele and by this reason the polymorphism was implicated in the pathogenesis of endometriosis. *CYP19* encodes cytochrome P450, a major component of aromatase. Aromatase is a key enzyme in the conversion of androgens to estrogens, and mediates the rate-limiting step in the metabolism of C_{19} androgens to estrogens. Different polymorphisms of *CYP*19 are present in the gene and have been related to variations of aromatase activity. A polymorphism C1558T (rs10046/C19T) has been correlated to the level of aromatase mRNA in breast tumor cells.[38]

Eight studies on *CYP17*A1 T-34C polymorphism in endometriosis have been published. Hsieh *et al.* (2004) [39] and Bozdag *et al.* (2010)[40] found association of *CYP17* and endometriosis in Taiwanese women. However, Kado *et al.* (2002),[36] Asghar *et al.* (2005),[41] Huber *et al.* (2005),[42] Juo *et al.* (2006),[34] De Carvalho *et al.* (2007) [43] and Vietri *et al.* (2009) [44] and found no association of *CYP17* polymorphism with endomentriosis. Seven studies were performed on different *CYP19* polymorphisms. Kado *et al.* (2002),[36] Arvanitis *et al.* (2003),[45] Vietri *et al.* (2009) [44] and Yang *et al.* (2010) [13] found positive association of different *CYP19* polymorphisms with endometriosis but Huber *et al.* (2005) [46] and Tsuchiya *et al.* (2005) [4] found no association.

Huber *et al.* (2005) [42] performed a study on ten polymorphisms associated to estrogen metabolism in 32 patients with endometriosis and found association of *HSD17* vlV A->C polymorphism to endometriosis. Tsuchiya *et al.* (2005)[47] also found a positive correlation between A allele of (Ser312Gly, A/C, rs) of *HSD17* polymorphism and endometriosis in a Japanese population. Lamp *et al.* (2010) [16] found a positive association of A allele of polymorphism (rs 605059, G937A) of *HSD17* with endometriosis.

Progesterone

Progesterone is a potent antagonist of estrogen-induced proliferation in the endometrium and may play a pivotal role in the pathogenesis of endometriosis, once progesterone acts by increasing the volume of the cells which line the wall of the uterus, enhancing the thickening of the endometrium and leading to its intense invasion by blood vessels.

The human progesterone receptor gene (*PR*) is located at chromosome 11q22-23 (MIM 607311/GenBank 15716) and has two isoforms which modulate the biological action of progesterone: isoform A that is capable of inhibiting the activation of the estrogen receptors, and isoform B that has the capacity of activating them.[48] The two

isoforms of *PR* were, in fact, products of the same gene, but of different promoters. PRA is composed of 765 amino acids, whereas PRB contains additional 128–165 amino acids inserted at the NH2-terminus of the molecule.[12]

Several polymorphisms have been described for this gene, among which one stands out: a polymorphism named PROGINS (rs1042838) that arises due to a gene insertion process of the *Alu* element into intron G between exons 7 and 8 of isoform A of the *PR* gene, producing an increase of 306 bp in the gene product.[49] The PROGINS polymorphism produces a decrease in the stability of the receptor, leading it to lose its capacity to inhibit the activation of the estrogen receptors, causing an inadequate control of these receptors, and thus exposing the endometrium to a greater action of estrogen.[50]

It is believed that, under the action of PROGINS, isoform A could also lead to an increased expression of isoform B (responsible for the activation of the estrogen receptors) and thereby contributing to a higher oncogenic action of this polymorphism.[50] Progesterone is involved in the regulation of the extracellular matrix metalloproteinases, stimulating the inhibiting factors of these enzymes, and acts also on the expression of angiogenic factors and on the cell cycle regulating factors.

Several authors have supposed the association of *PR* polymorphism PROGINS, and endometriosis. Wieser *et al.* (2002),[51] Lattuada *et al.* (2004),[52] and Carvalho *et al.* (2007) [43] in their studies demonstrated a significant correlation between the PROGINS polymorphism and endometriosis. On the other hand, Govidan *et al.* (2007) [53] in their studied concluded that the PROGINS polymorphism can be considered as a risk marker for breast cancer, but not for endometriosis and uterine fibrosis. In 2007, van Kaam *et al.*[54] studied 72 women with endometriosis, 40 women with adenomyosis in the uterine wall, 102 gynecological patients without symptomatic endometriosis and 93 healthy females and concluded that PROGINS polymorphism does not seem to modify the risk of deep infiltrating endometriosis. However, D'Amora *et al.* (2009) [55] observed that PROGINS variant may influence cell proliferation, viability, and apoptosis in endometrial cell metabolism.

Our group [56] determined the frequency of the PROGINS polymorphism in women with endometriosis-associated infertility, infertile women without endometriosis and controls. The data suggest that PROGINS is not related either to endometriosis-associated infertility, independent of stage, or to idiopathic infertility in the Brazilian population studied.

Finally, an international collaborative study (2011) [57] investigated the association between self-reported endometriosis and the putative functional promoter +331C/T single nucleotide polymorphism and the PROGINS allele in 5812 white female controls, of whom 348 had endometriosis, from eight ovarian cancer case-control studies (An international ovarian cancer consortium including studies from Australia, Europe, and the United States). The occurrence of endometriosis was reduced in women carrying one or more copies of the +331 T allele, whereas there was no association between the PROGINS allele and endometriosis.

Luteinizing hormone

During adult life, until menopause, the luteinizing hormone (LH) has an important role in the development of follicle and maturation of the oocyte, promoting ovulation and luteinization of the ovarian follicle. Besides, it stimulates the production of androgen and together with FSH (Follicle-Stimulating Hormone) regulates the production of the steroid sex hormones estradiol and progesterone by theca cells that surround growing follicles in the ovary and maintaining the progesterone production of the corpus luteum.[58]

The association between LH levels and endometriosis has been for long suggested. Cheesman *et al.* (1982) [59] observed an abnormal LH profile in urine samples from 26 of 29 infertile patients with endometriosis.

Chew *et al.*. (1990) [60] observed elevated peritoneal fluid LH concentration in infertile women with endometriosis.

Furthermore, Ronnberg *et al.* (1984) [61] demonstrated that, in patients with endometriosis, the LH receptor (LHR) concentrations in ovarian follicles and corpora lutea were lower during the early and late follicular phase and the late luteal phase of the cycle than those seen in control subjects. In patients with severe and extensive endometriosis, the LHR concentrations were extremely low. In addition, Hudelist *et al.* (2008) [42] showed enhanced expression of LHR on the surface of endometriotic implants when compared to control samples.

Endometriosis is associated with alterations in the hypothalamus-hypophysis-ovary axis, with alterations resulting thereof in the concentrations of hormones FSH, LH, estradiol and progesterone in serum, peritoneal fluid and follicular fluid of women with endometriosis. The association of endometriosis with alterations in the neuroendocrine axis suggests an abnormality in the follicular function, with altered LH concentration, reduced fertilization capacity of the oocyte and altered luteal function.[62, 63]

In fact, it has been reported that granulosa cells of the pre-ovulatory follicles of infertile women with endometriosis are less sensitive to the luteinizing hormone[64]. A significant reduction in aromatase activity in the follicles of women with endometriosis might explain the smaller production of steroids by the follicle.[65] Taken together, all these data show that the follicles of women with endometriosis present severely impaired steroidogenesis. Obviously, altered steroidogenesis can affect the oocyte function, which might explain the ovulatory dysfunction, the impaired fertilization and defective implantation, parameters frequently associated to endometriosis.[66]

LH belongs to the family of glycoprotein hormones. Structurally, LH is a heterodimer consisting of two dissimilar subunits: the α-subunit and the hormone-specific β-subunit (MIM ID +152780/GenBank ID 000894.2). The intact heterodimer structure is required for appropriate biological activity (Pierce and Parsons, 1981). The LHβ-subunit gene is located on chromosome 19q13.3 (www.ensembl.org).

Few mutations linked to endometriosis have been described at *LH*β-subunit. The most common genetic variant of the *LH*β gene is G1502A (rs5030774), which results in amino acid substitution of serine for glycine at position 102. This substitution may have a potent effect on LH function. Because glycine and valine are important components in the formation of hydrophobic regions in a protein and serine has a polar side chain, the replacement of glycine by serine at position 102 introduces a hydrophilic force in the molecule. This change affects the normal conformation and function of LH, leading to lower receptor-binding activity and lower biopotency for progesterone production than wildtype LH.[67]

Liao *et al.* (1998) [67] showed that the *LH*β G1502A polymorphism was higher in infertile women with endometriosis and suggested an association between these mutations and infertility, especially endometriosis-associated infertility. Mafra *et al.* (2010) [68] in a study of 110 infertile women with endometriosis, 84 infertile women without endometriosis and 209 healthy fertile women confirmed the association of the polymorphism to infertility and minimal/mild endometriosis-associated infertility. However, this variation was not found either in Korean or in English women with endometriosis.[69, 70]

Hypothetically, the presence of the LH variants could explain the endocrinological and menstrual changes observed in women with endometriosis.

Androgen receptor

The androgen receptor (*AR)* gene is located on the X chromosome at Xq12. This gene is more than 90 kb long and codes for a protein that has 3 major functional domains: the N-terminal domain, DNA-binding domain, and androgen-binding domain. The protein functions as a steroid-hormone activated transcription factor. Upon binding the hormone ligand, the receptor moves to

the nucleus and then stimulates transcription of androgen responsive genes. This gene is involved in various biological processes such as sexual differentiation, maturation, and spermatogenesis.[71]

The *AR* gene contains 2 highly polymorphic trinucleotide repeat segments that encode polyglutamine and polyglycine tracts in the protein, whose length and methylation pattern affect both *AR* expression and function.[72]

An increase in androgen receptor, caused by estrogen is recognized as one of the biological phenomena related to estrogen-induced growth in uterine endometrium.[73] Besides, the *AR* expression is present in the endometrial tissue and the pelvic organs, which are the targets for endometriotic implants. Based on its physiological function, genetic variations on AR could contribute to the development of endometriosis. In fact, the *AR* expression was detected in endometriosis, adenomyosis, and endometrial carcinoma.[74]

The role of genetic variants of *AR*, as the (CAG)n repeat alleles of the exon 1 have been correlated with the risk of developing endometriosis. Hsieh *et al.* (2001) [71] investigated 110 Chinese women with endometriosis and 99 controls and found a statistically significant difference in the distribution of CAG repeats in population with or without endometriosis. In an Indian population, Shaik *et al.* (2009) [75] found a positive correlation between the number of repeats and endometriosis and leiomyoma, in a research performed on 331 subjects, including 90 women with endometriosis, 140 women with leiomyoma and 101 healthy women. Besides, Tong *et al.* (2010) [76] in a study with 74 women with PCOS and endometriosis and 141 controls from a Chinese Ham population found a positive correlation between the number of repeats and endometriosis, suggesting the polymorphism can be considered a marker of the disease.

On the other hand, Lattuada *et al.* (2004) [72] in a study with 107 Italian women with endometriosis found no difference in the number of AR-CAG repeats between women with endometriosis and controls.

Endocrine disruptors in the endometriosis

Environmental chemicals, known as endocrine disruptors, are composts that have the capacity to mimic, block or modulate the endocrine system through the interaction with steroidal receptors. Recently evidences have proposed a putative role for ubiquitous environmental contaminants in the occurrence of endometriosis.[77]

Osteen *et al.* (2005) [78] and Igarashi *et al.* (2005) [79] demonstrated that co-exposure of primary cultures of adult stromal cells and endometrial epithelium to TCDD decreased the expression of progesterone receptor B (PR-B) and A (PR-A) (PR-A/PR-B) in stromal fibroblasts and increased expression of metalloproteinases in both the endometrial stroma and the epithelium. Furthermore, the offspring of mice exposed to TCDD showed abnormal expression of progesterone and deregulation of fertility over three generations without any additional exposure to endocrine disruptor,[80] suggesting an epigenetic inheritance change.[81] The exposure to TCDD affects not only steroid receptor levels and gene expression, but can also affect the metabolism of steroid hormones and serum transport.[82]

Exposure to progesterone during the secretory phase of menstrual cycle promotes the negative regulation of endometrial matrix metalloproteinases, thereby preventing damage endometrial after menstruation. Therefore, environmental substances that interfere with the action of progesterone alter the endometrial microenvironment promoting an inflammatory process similar to the loss of endometrial tissue during menstruation.

In Belgium, Koninckx *et al.* (1994) [83] 46 found that the prevalence of endometriosis in infertile women was 60 to 80% and that concentrations of TCDD in milk from that country is among the highest in the world.[84] Pauwel *et al.* (2001) [85] conducted a case-control study in Belgian women and found an increase of endometriosis associated with elevated serum levels of dioxin compounds and derivatives. This study provided one of

the most important evidence that the population development of endometriosis may be related to toxic effect of TCDD.

Besides, Cobelli *et al.* (2009) [86] investigated the concentrations of bisphenol A and B in the serum of 58 women with endometriosis and 11 fertile women without the disease. High concentrations of bisphenol A and B were present, respectively, in 51.7% and 27.6% of women with endometriosis and no women in the control group. The compound bisphenol A and/or B was present in the serum of 63.8% of women with endometriosis, suggesting an important relationship between exposure to bisphenol A or B and endometriosis.

The interaction between bisphenol A and/or B with estrogen receptors produces activation of the same transcription factor 17-β-estradiol,[87] located near the promoter region of the aromatase gene. This mechanism probably determine aromatase activity and hence estrogen production, favoring proliferation and inflammatory characteristics of endometriosis. Moreover, previous studies have demonstrated a relationship between increased serum concentrations of bisphenol A and its metabolites, altered secretion of gonadotropin hormones and increases androgenic hormones.[88]

Epidemiological studies of the effects of endocrine disruptors in endometriosis are difficult to achieve because there are several obstacles. Serious problem is the mixture of different agents with estrogenic, antiestrogenic and antiandrogenic potential in the environment. Another issue is the limited knowledge about the time between exposure and effect in the body. For the majority of adverse effects, the critical window of exposure (the fetal, perinatal, pubertal or adult) has not yet been identified. Moreover, epidemiological research can often be influenced by factors such as selection of study area, sample size, choice of limit values, the substance studied, among others.[77]

Thus, the relationship between endocrine disruptors and endometriosis is complex. The exact mechanism of action of endocrine disruptors has not been fully elucidated, but it is believed that these substances can lead to epigenetic modification and result in altered gene expression.

Conclusions

The proliferation and differentiation of the endometrium are mediated mainly by estrogen and progesterone. However, luteinizing hormone, androgens, endocrine disruptors and genes affecting the metabolism of sex hormones are also potential candidate genes to influence the development and progression of the endometriosis.

Polymorphisms, in most of cases, are not direct cause of diseases, but can be considered components in the study of multifactorial disorders. Finding genetic variants contributing to complex diseases such as endometriosis is far more difficult because the contribution of individual genes is small, many genes contribute to an individual's risk of developing the disease and disease risk is often modified by environment. Many studies are required for both the discovery and replication steps with sufficient power to detect the small effects of any individual variants. Most of the published studies regarding endometriosis have used heterogeneous control groups, such as healthy men and women, newborns, umbilical cord blood and menopausal women. Another important factor to consider is the heterogeneity of symptoms in patients with endometriosis: asymptomatic, pain, infertility, pain and infertility. This variation represents different spectrum of the same disease? Or are they different diseases? It is difficult to correlate data from heterogeneous studies regarding the ethnicity and the selection of patients and controls, and methodology. The identification of reliable genetic associations is important to achieving the results of genomic research to clinical application. To do this requires the collaboration of researchers in the evaluation of data and summary of results found in several studies for the creation of a research network for the recognition of genetic associations more creditable.

Therefore, identifying critical combinations of genetic variations conferring additive risks of developing endometriosis would be of clinical interest for identifying women most likely to benefit from surgical and pharmacologic interventions.

Riassunto

L'effetto degli ormoni sullo sviluppo dell'endometriosi

L'endometriosi è una patologia ginecologica frequente in cui il tessuto istologicamente simile all'endometrio, con ghiandole e/o stroma, cresce al di fuori della cavità uterina e può portare a dolore pelvico, dismenorrea e infertilità. I fattori genetici esercitano un'influenza notevole su molti aspetti della funzione riproduttiva femminile e in numerosi studi si è cercato di identificare i geni di suscettibilità per i disturbi che interessano la fertilità femminile, come l'endometriosi. L'importanza degli ormoni steroidei nell'endometriosi è indiscutibile. La patologia è più diffusa nelle donne in età riproduttiva e regredisce dopo la menopausa e non ne è stata segnalata la presenza prima del menarca. Gli steroidi sessuali, gli estrogeni e il progesterone vengono prodotti principalmente nelle ovaie e regolano la crescita del tessuto endometriale, sostanzialmente stimolando e inibendo rispettivamente la proliferazione delle cellule. In aggiunta, gli estrogeni rivestono un ruolo importante nella regolazione del ciclico rilascio delle gonadotropine e nella follicologenesi. Per dimostrare l'interazione degli ormoni e dei loro recettori con l'endometriosi sono stati condotti numerosi studi con risultati contrastanti . Inoltre sostanze chimiche ambientali, note come interferenti endocrini, sono in grado di imitare, arrestare o modulare il sistema endocrino attraverso l'interazione con i recettori steroidei. Recenti evidenze hanno suggerito il ruolo putativo dei contaminanti ambientali nell'insorgenza dell'endometriosi. In questa review presentiamo articoli significativi riguardanti l'interazione tra endometriosi, ormoni e varianti genetiche polimorfiche.

Parole chiave: Endometriosi - Infertilità - Estrogeni - Progesterone - Ormone luteinizzante.

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