Chapter

Potential Therapeutic Options and Perspectives for Alleviation of Endometrial Estrogen Dominance and Progesterone Resistance in Endometriosis

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Abstract

Endometriosis is a chronic disease, influenced by internal and external environment, with long duration from intrauterine life with acme during childbearing, when it is associated to chronic pelvic pains, and infertility/subfertility. DNA hypermethylation of endometrial promoter PRs *Hox genes* and DNA hypomethylation of promoter ERβ *gene* is a possible explanation of estrogen dominance, progressive loss of progesterone signaling, followed by progesterone resistance in ectopic, and progesterone attenuance in eutopic endometrium, for failure of hormone therapy (HT), repeated recurrences after surgery, cancers after long time evolution. Animal models, human trials demonstrated progesterone (P4) and progestins influences over progression of disease pathological characteristics, associated to endometrial ER, PR aberrant expressions: ERα loss, and abnormal PRB/PRA *ratio*. P4 supplementation before mice induced-endometriosis protected from PRs depletion, action that can be translated in women according to the difference of 7 to 12 years between histologic onset and clinical symptoms/signs, parallel to progressive loss of PRs and PR-mediated signaling in ectopic and eutopic endometria. The animal studies have shown that a DNA methylation inhibitor alleviates lesion growth, and induces PRs target gene expression restoration. Continuous/extended contraceptives, dienogest-a new progestin, GnRH agonists/antagonists, aromatase inhibitors, SERM, SPRM, combinated molecules are therapeutic options/perspectives aiming restoration endometrial estrogen-progesterone balance, without disease's cure. HT may be active alone, or surgery associated.

Keywords: endometriosis, estrogen dominance, progesterone resistance/attenuance, timing, progesterone/progestins, DNA methylation inhibition

1. Introduction

Urgent innovations are demanded in endometriosis management, which should start by deeper undestanding of disease core features, with disease different phenotypes and idiosyncrasies. Endometriosis, a chronic inflammatory and immune disease, dependent on environement factors, genes- *Hox* genes

code (HOXA10/HOXA11), epigenetics, and ovarian steroid hormones, with their receptors and coregulators in the eutopic endometrium and ectopic sites, was demonstrated to have a long duration of progress from intrauterine life, latency in childhood, and acme during reproductive years [1–3] with reappearance in postmenopause when hormone replacement therapy, or even without [4]. This fact permits therapeutic intervention to correct endometrial abnormal functions during menstrual cycle, to prepare decidua receptivity for successful egg implantation in women with minimal or mild to moderate endometriosis, in order to avoid the severe stages, and lack of response to therapy, considering that progesterone resistance is an acquired property of eutopic endometrium [5]. The therapeutic aims are to prevent, or at least to stop the progressive damages induced by ectopic endometriotic lesions in the uterus, entire genital tract, and in extra-uterine sites by the endometrial mezenchymal stromal/stem/progenitor cells with their specific migratory, adhesive, and invasive properties, with their genome changes when are outside the uterus, to influence the self- protected endometriotic lesions [6] and to ensure a normal eutopic endometrial cycle functioning, with normal ovarian steroid hormones receptors distribution during menstrual cycle. The aims can be individually accomplished if therapy is started from early stages of illness, by moving from pure hormonal therapy to drug combination, or novel molecules- SERMs, SPRMs which can escape the disrupted homeostatic mechanisms characteristic for endometriosis [7].

One may propose and discuss a perspective "timing" of endometriosis treatment, to maintain or for an early restoration of endometrial estrogen- progesterone receptors natural balance [8] being recognized a still delay in diagnosis, and treatment [9] delay that permits the evolution of genital damages by progressing endometriosis, and in time the risk of atypical endometriosis, and cancers which is very difficult to be assessed clinically, without specific biochemical markers [10].

The incidence of endometriosis of one case in 10 women of reproductive age [11, 12] or around 17% [13] is increasing when one assseses infertility and chronic pelvic pains - up to 50% [14] respectively up to 60% [15] recently being estimated 176 million women worldwide, making endometriosis as common as diabetes mellitus [16].

There are three distinct forms of disease according to ectopic sites of endometrial-like tissue location (peritoneal, ovarian and rectovaginal endometriosis), each of them being associated with specific symptoms, although dysmenorrhea, and chronic non-menstrual pelvic pains, dyschezia, dyspareunia are the most frecquent [17]. The literature makes some differences regarding the score of endometriosis, namely the ENZIAN classification/score describes superficial (less than 1 mm), intermediate (2 to 4 mm), deep (greater than or equal to 5 mm), and very deep implants (greater than 10 mm) [18]. The ENZIAN score was proposed of the revised American Society of Reproductive Medicine score (1996) [19], which was demonstrated to be less adequate to clinics, and the ENZIAN score was recently reviewed by experts in imagistic and surgical diagnosis [20]. So endometriosis has a similarity to oncology with 4 stages of evolution, with the difference of missing nuclear atypia [21] but with possible evolution to malignancy in 1% cases [1, 22] or further it may be associated to hematopoietic and breast cancer (HR of 1,3–95% CI 1.1–1.4, in Swidish women) [23] and ovarian cancer, – OR of 1.73, (95% CI: 1.10–2.71) on a pool of women from different continents- Australia, Canada, Denmark, USA, during 10 years (1989–1999) with previous endometriosis [24]. The natural history of endometriosis is uncertain, e.g. it is not known whether superficial peritoneal endometriosis (SPE) can progress to become another subtype, regress spontaneously, or whether disease progression (or lack of treatment) can lead to problems with infertility, and there is poor correlation between pain severity and the amount, location, and subtype of the ectopic lesions [16].

The literature does not mention a conclusive noninvasive diagnostic available tool to allow early detection of endometriosis, the delay in detection being of 7–12 years of latency from symptoms onset to the definitive diagnosis, and even in the best medical centres the full extent of the disease may be unknown [25] and up to 2017 it was not identified any fully validated, symptom-based, patient- reported questionnaire for endometriosis screening in adult women with potential endometriosis [26]. One must think to endometriosis in adolescent girls with family history, abnormal characteristics of menstrual cycles with the aim to avoid the structural and functional abnormalities progression induced in women's endometrial genes - mainly *Hox* codes for steroid hormones receptors, ligands, and co-regulators.

The next pages will discuss concepts, theories or hypothesis of potential therapeutic options and perspectives for prevention, normalization or restoration the endometrial estrogen- progesterone balance, and their receptors in the epithelium and stroma, because many years there were recommended ovarian supressing drugs, and surgery.

2. Endometrial phenotypes in endometriosis

The interest for diagnosis and therapeutic success connected to side effects, limitations and failure rate of different classes of medication, and high risks of recurrence after surgery or medication discontinuation imposed the analysis of endometrium phenotypes, proliferative and differention *in vitro* capacities of stromal cells from ectopic lesions of peritoneum, ovaries, and deeply infiltrating endometriosis in comparison to the same structures of normal women, using the new techniques as contrast microscopy, immunocytochemistry, functional bioassays [27] and RT- qPCR of endometrial genes.

The study of Burney et al. [28] analyzed eutopic and ectopic endometria comparative to non ill women, and it was demonstrated a molecular phenotype of attenuated progesterone response within eutopic endometrium, from the dysregulation of numerous genes which are progesterone regulated, and the progesterone resistant phenotype is more frecquent in ectopic endometrium comparative to non-ill cases. This condition is associated to a pro-inflammatory phenotype [29, 30] which increases both estrogen dominance, and progesterone resistance. The eutopic endometrium of ill women has an attenuate response to P4 because estrogen-responsive genes are not suppressed in their stromal cells in early secretory phase of menstrual cycle comparative to normal [28, 31, 32]. The British and Italian doctors' conclusion [29] was that endometriotic cell lines, and stromal eutopic endometrial cells in ill-women are lossing the capacities of differentiation, and respectively of deciadualisation, aspects that explain cells capacities for proliferation and survival in the ectopic environment, and high infertility/subfertility rates. Deep endometriosis appears to be a special type, because predominance of PR less active isoform (PR-A) over the full length, due to epigenetic abnormalities affecting PR gene transcription, associated to oxidative stress, facts that induce a condition of more resistant to size regression upon medical treatments [7].

3. Concepts on endometrial peculiarities, as a steroid hormones target in endometriosis. Estrogen dominance. Progesterone resistance. Progesterone attenuance

The efficacy of endometriosis therapies may be improved by dissecting the unique molecular properties of eutopic and ectopic endometria compared to normal

endometrium. At first glance, the terms "estrogen dominance" and "progesterone resistance" appear to describe opposite sides of the same coin [6]. Endometrial Progesterone Resistance is described since many years [33] as there are other hormones resistance, being first named as "Pseudocorpus Luteum Insufficiency" [34] meaning that endometrium is not able to respond to bioavailable P4 plasma levels inbetween normal limits. In non-ill women E2 induces epithelial proliferation to build endometrial thickness during the proliferative phase of the menstrual cycle, then P4 inhibits E2-induced proliferation and allows stromal cells to begin decidualization during the secretory phase [35] in order to prepare the stroma to become receptive to blastocyst invasion during "window of receptivity/implantation" in normal, fertile women [36].

3.1 Dysregulation of endometrial steroid hormones receptors in endometriosis

The molecular mechanism triggered by ovarian steroid hormones in endometrium is well known: steroid hormones link to specific nuclear (ERα, ERβ; PRA, PR-B, with specific ratios between them), cytoplasmic (ERβ), and membrane receptors (non- canonical G protein-coupled estrogen receptor (GPER) [37] and PGRMC-1 and PGRMC-2), which are able to bind to the promoter of the target genes, being up- or down- regulated by their co-activators (SRC-1, SRC-2, SRC-3 for estrogen receptors- ER) or downstream effectors (TGFβ, Dickkopf-1, retinoic acid, c-*myc*, *etc.* for progesterone receptors- PRs) [28] and influence endometrial cells proliferation and differentiation [38]. Endometrial repair after menstruation, proliferation and/or differentiation processes are dysregulated in endometriosis when menstrual reflux with endometrial stromal and epithelial glands cells with their exosomes migrate, adhere and invade peritoneal surface and/or other ectopic sites, associated to waves of inflammation (by systemic and local reactive responses to the presence of endometrial debris), neuro- angiogenesis and neuroinflammation, and aberant scar formation through fibrosis and adherences (possible a self-protection mechanism for ectopic lesion, as in chronic infections) at every ovarian cycle (different from normal endometrium restoration after each menstrual cycle). All these events are genetic controlled, epigenetic changed by hyper (for PR promoter) or hypomethylation (for ERβ) of DNA steroid hormones receptors promoters [39–41]. When the tightly regulated balance of epithelial- stromal P4 and E2 signaling is lost, P4 resistance and E2 dominance are prone to ensue, as in endometriosis [6]. P4 resistance may lead to both increased lesion growth and a non-receptive endometrium, and actually one speaks also about progesterone attenuated response in eutopic endometrium, which is associated to infertilty/subfertility. Estrogen dominance, progesterone resistance and progesterone attenuance in the ectopic and eutopic endometrium are explained by the dysregulation of estrogen and progesterone receptors their genes (*ESR1* and *ESR2*) [32]; a single gene- *PRG* for PRs) [42] with their micro-RNA (miRNA) –the cells' critical regulators for development, and physiology, their mis-expression being associated to pathology [43].

When dysregulation condition persists it leads to both increased lesion growth and progression to a superior stage, and a non-receptive endometrium. P4 acts on stromal cells of the normal endometrium, inducing paracrine factor(s), and they induce the expression of the enzyme 17β-hydroxysteriod dehydrogenase type 2 (17β-HSD-2) for metabolization of E_2 to estrone (E_1), in the epithelial cells, and cell proliferation arrest. Excess E2 with Estrogen Dominance, and Progesterone Resistance are well documented in ectopic endometrium with aberrant levels of ERs and changed ER-α/ ER β *ratio*, where the genes analyses have proved to become an acquired property, through their migration and exposure process to

peritoneal environement [5]. ER-α and ER- β have essential roles in establishment and progression of ectopic lesions [32]. ERβ is excessively expressed in stromal cells of the ectopic lesions, versus non-ill women, fact due to hypomethylation of ERβ promoter, which contributes to low ER-α expression in ectopic endometrium [41, 44]. ERβ protein net -work together with SRC-1 coactivator isoform with which it cooperates, may have a cytoplasmic, non-genomic action in endometriosis as Han SJ, Jung SY, Wu SP, et al. discovered [44] (**Figure 1**).

Eutopic endometrium may prove the same endometrial dominance and progesterone resistance, but after some years of disesease evolution, being described cases with initial progesterone attenuance in eutopic endometrium and progesterone resistance in the ectopic sites, usually in deep endometriosis [28]. It is documented a local increased synthesis of estrogen [45, 46] not a systemic high level [47] through the presence of the enzymens (aromatase, and 17β-hydroxysteroid dehydrogenase-1, 17β-HSD-1) [48, 49] and a blunted response to progesterone in eutopic and ectopic endometrium, P4 serum levels being similar to non- ill women [45]. In human and experimental mice the ER-α content may be normal in eutopic endometrium, as in non ill women, but ER β are increased in both epithelial and stromal endometrial cells of eutopic and ectopic sites, as PRs levels are reduced in eutopic endometrium and PRs are lost in ectopic sites [44]. A recent analyses of ERs in deep endometriosis revealed that ER-α is a subtype for this condition [50] ER-α levels being predictive for symptoms severity, and for responses to treatment [51]. Progesterone attenuance of eutopic endometrium is connected to altered endometrial receptivity in the "window of receptivity/implantation" and to a significant reduction of implantation rate in ill-patients trying *in vitro* fertilization, due to stromal cells impair decidualization proved by a reduction of nearly 2-fold in IGFBP-1, and of leukemia inhibitory factor (LIF) [52] and to reduction/dysregulation of P4 target genes during the "window of receptivity/implantation", time when normally, the endometrium is exposed to the highest levels of P4 [53] as it is strikingly down-regulated *glycodelin*- the prototype progesterone-responsive gene, in eutopic endometrium of ill-women compared to non-ill [53, 54]. LIF low levels are an intrisic glandular dysfunction, induced by the gland-specific transcription factor Forkhead box A2 (FOXA2) low level [55, 56] also a P4 gene target. There are contradictions on the status of ERs and PRs in ectopic endometrium – an ERs increased expression, or others show reduced expression of both ERα and ERβ

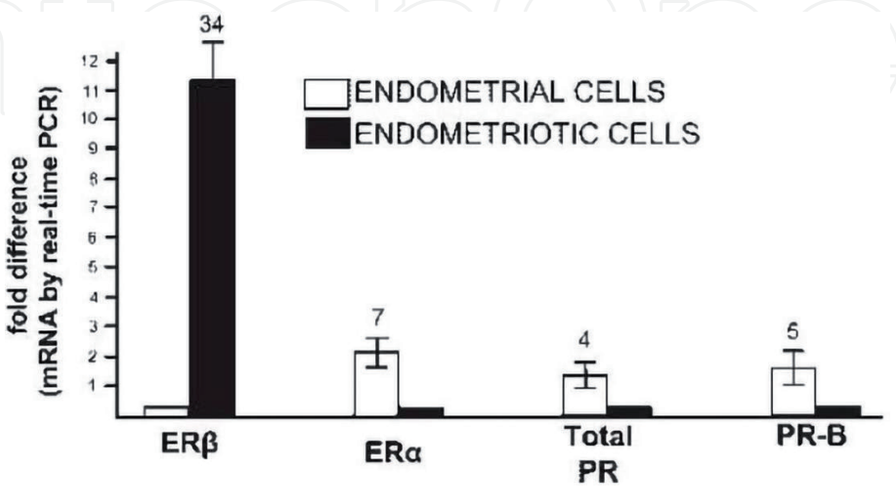

Figure 1.
Role of ER-β in endometriosis. microRNA levels of steroids in primary stromal cells isolated from endometrium and endometriosis (n = 8 patients in each category). Comparable in vivo differences were also observed between whole tissues of endometrium and endometriosis Legend: ER: estrogen receptor; PR: progesterone receptor; real time-PCR: polymerase chain reaction (adapted from Bulun et al. [45]: open acces).

[57–59] and lower levels of PRs [5, 60]. The eutopic endometrium has an attenuate answer to P4, the isoform PR- B is not expressed in patients' endometrium, being only the isoform PR-A, because progesterone-responsive genes are not deleted in eutopic endometrium in comparison to normal women in the early secretory phase of cycle [28–32], a normal PR-A/PR-B *ratio* is very important in endometrial function. One may consider that the relative differences between studies regarding the PR isoforms loss in ectopic and eutopic endometrium may be explained by stage of disease, type of lesion and cells, and method of analysis.

Previous studies [32] demonstrated in experimental mice that high levels of ERα are driving proliferation, adhesion and angiogenesis in ectopic tissue, and also modulate inflammation, and ERβ prevents apoptosis and enhance invasion, proliferation, adhesion, and inflammation to stimulate the growth of ectopic lesion, so both isoforms might sinergistically contribute to regulation of proliferation, adhesion, and inflammation in endometriotic lesion. These discrepant findings are explained by the differences in study design, patient selection criteria, cycle stage, and endometriosis type and stage. Similar to these contradictory results on endometrial steroid hormones receptors is the situation with miRNA indentification by real-time quantitative reverse transcription-polymerase chain reaction (real time qRT-PCR) in normal endometrium, eutopic and ectopic sites, connected to mi-RNA upregulation (over expression) or down regulation (under expression) in eutopic and in different ectopic areas (peritoneal, ovarian), and some are "mis-expressed" endometriosis [61]. There are differences between authors, with conflicting reports on whether or not miRNA expression was influenced by the menstrual cycle phases, endometrial cell type, miRNA type, level in ectopic/eutopic tissue, and stage of disease.

3.2 High micro-heterogeneity of endometrial steroid hormones receptors signaling in endometriosis

Normal endometrium is containing large quantities of distinct stromal cells with abundant estrogen-induced PRs, which influence glandular epithelial cell proliferation and differentiation, and protect against carcinogenic transformation, when PRA/PRB are in a proper *ratio* to ensure normal P4 response. PRA and PRB are members of a superfamily of almost 50 ligand-activated nuclear transcription factors [62]. *In-vitro* studies suggest that the two PR isoforms differ functionally, and that their relative expression in a target cell may determine the nature and magnitude of response to P4. The two isoforms are in comparable levels expressed in proliferative phase, but in the mid- secretory only PR- B is present in the epithelial glands, PR-A is predominantly present in the stroma throughout the cycle. It is a homogeneity in the relative expression in PR-A and PR-B in adjacent cells within the same tissue compartment, and a heterogeneity between glands, observed under some circumstances in the endometrium functionalis, suggesting that PR isoforms down-regulation by P4 is asynchronous, and between the glands of the basalis and functionalis of the endometrium implying region specific responses to hormonal stimuli [63].

A recent European study on deep endometriosis [64] showed a high variability of ERα and PR distribution in the same gland, among distinct glands of the same sample, and among distinct patients receiving the same treatment. Luminal epithelial height variability was primarily due to epithelial cells heterogeneity in a gland, secondarily to the glands randomaly evaluated on the same section, and tertiary to the patient category. The heterogeneity of ERα and PR distribution in the same women could explain why endocrine treatments are unable to cure deep endometrios. The cause of heterogeneity in endometriotic tissues is difficult to be ascertain, one hypothesis being the DNA methylation of the steroid hormones [65] or of their promoters [39, 40] or

an abnormal proteolysis of steroid hormones chaperons [66], the co-chaperons are required by PR for signaling uterine cycles and implantation [67].

Mice induced endometriosis demonstrated a high inter-animal variation in the levels of ERs, PRs, in ectopic endometrium vs. controls; with variable levels by almost 100-fold within the same lesion, and with differences between two lesions from the same animal [68] aspect called "micro-heterogeneity". The changes are tissue intrinsic, and some researchers propose that the variable outcomes in hormonal therapy for endometriosis could be possibly due to heterogeneity or polymorphism in the expression of steroid hormone receptors in the ectopic endometrium [68] or in all endometrial locations- eutopic, and ectopic, being known the heterogeneity of PRs in glands, and the homogeneity of PR isoforms in stroma of normal human endometrium [63] making the magnitude in response, the attenuance, and the resistance in response to P4, independently to the serum levels of P4 [69]. This intrinsic biologic alteration of eutopic endometrium explains the missing differences in endometrial thickness, and histology –respectively luteal differentiation, or epithelial integrin expression at the lower mid-luteal serum progesterone level (as 3–4 ng/ml) in programmed cycles of physiological and subphysiological exogenous progesterone replacement in GnRH agonist-suppressed healthy volunteers. One may consider that these results are an answer to the questions whether the abnormalities of eutopic endometrium in early secretory phase suggestive of attenuated progesterone response in the transition from proliferative to secretory phase are due to lower level of circulation or local bioavailable progesterone or to the changes in endometrial transcriptome, with dysregulation of progesterone- regulated genes.

3.3 Nuclear receptor coregulators in the modulation of progesterone and estrogen signaling in endometriosis

Endocrinologic literature presents different series of nuclear receptors coregulators,- proteins that intervene to modify chromatin structure and regulate large-scale gene transcription programs by forming large complexes with the nuclear receptors of the target cells [70]. In the female genital tract the *PRG* and *ESR1* are critically regulated by a family of regulatory proteins named steroid receptor coactivators (SRCs) - SRC-1, SRC-2, and SRC-3, the first nuclear receptors coregulators are involved in the balance between E2 and P4 in human endometrium. SRC-1 down regulates P4 target genes in the epithelium, and up regulates them in the stroma; SRC-2 is necessary for human endometrial stromal cells decidualisation [71] for P4 signaling and for ESR1 signaling; the transcriptomic analysis revealed that 50% of SRC-2-regulated genes are also regulated by P4 [72] and it is critical for murine uterine function; ablation of SRC-2 induces partial loss of decidualisation and infertility, and both SRCs ablation induces complete loss of decidualisation [73, 74].

4. Potential therapeutic options to maintain/restore endometrial normal estrogen-progesterone signaling in endometriosis

Presently pharmacotherapy mainly with hormones (Hormone Therapy- HT) and surgery are two cornerstones in endometriosis management. Surgery with histological confirmation of ectopic endometrial glands and stroma remains the gold standard for diagnosis [75, 76] surgery being generally reserved for patients who fail medical therapy, or who desire pregnancy, being usually performed by laparoscopy [77, 78]. Surgery is able to eliminate visible endometriotic lesions, without the cure of the disease [79], and majority of drugs are symptomatic, not cytoreductive [80]. Yet it is not known if surgery itself may be incomplete (*i.e.*, microscopic disease)

or if other factors, such as aberrant PRs expression of the eutopic endometrium influences recurrence [60] connected to the eutopic endimetrium transcriptome changes compared to non-ill women, indicating abnormalities that predispose to new implants in extrauterine locations after surgical excision of ectopic lesions [81]. Recurrence rate after surgery or medication discontinuation was recorded up to 45% after 5 years [82] and recently one discusses the translation from adjuvant therapy to tertiary endometriosis prevention in postoperative medical care [83]. The moment of medical therapy associated to surgery- before, after, or both before and after surgery is much analyzed, to maximize treatment response, but literature data is still inconclusive [84]. The HT goal is to induce atrophy of endometriotic lesions, even if one missis the ability to predict which medication each individual patient will respond to, being many attempts to find one or more predictive markers [85] to score HT, as it is the immunohistochemical Histo (H) -score on the PRs status, and CYP19A1 expression for the response to progestins, respectively for the need to block estrogen signaling [60]. The high H-score for PRs was proposed to be >80 (associated with 100% positive predictive value), and the low H-score ≤ 5 (associated to 94% negative predictive value), with some authors' comments regarding H-score usage: the score is useful for ectopic endometrium response to progestin- based therapy, not for eutopic endometrium, because the lack of score's correlation to eutopic endometrium. It is recommend to score PRs in the excised ectopic tissues, and to determine the reason for progesterone/progestins/COCs failure. When adhesions/fibrosis are predominant it is sure the non-response to HT, but some PRs expression may indicate an insufficient dosage of progestin or noncompliance with therapy (*i.e.*, inability to tolerate side effects), and for cases with low H-score, patients being PR resistant, it is advised to avoid progestins after surgery in favor of GnRH agonists or GnRH antagonists [86, 87], danazol- rarely used actually, or aromatase inhibitors.

Actual medical therapies allow suppression of endometriotic lesions, women require long term treatment [79] to maintain the benefits, to avoid recurrences, being recognized high rate relapse even after surgery. After surgery one must continue HT with contraceptive pills, or IUD [88] with the aim to preserve ovarian follicles reserve, and because ovarian aging, to try spontaneous pregnancy or ART.

Individual genetic characteristics can affect the bioavailability and pharmacodynamics of HT, mainly estrogen dominance and P4 resistance/attenuance, and, hence, explain part of the variability in the therapeutic response, as it is the polymorphism of CYP3A4/5 involved in levonorgestrel metabolism [89].

One can respond to therapeutic wishes by timing progesterone/progestins administration, and by moving from pure hormonal therapy to drug combination, or to novel molecules capable to restore the various homeostatic disrupted mechamnisms by disease. A number of potential therapeutics are currently in pre-clinical or early clinical studies, fact which may alter further treatment strategies.

4.1 Progesterone/progestins therapy

Kistner [90] was first who postulated that decidualisation observed during pregnancy might cause necrosis, and the consequent elimination of superficial ectopic implants, and this was the logical reasoning for progesterone recommendation, and use to control endometriosis. During pregnancy on assists at ovarian functions suppression, fact that is mimicised by HT in endometriosis [91]. After Kistner RW first initiave in the years 1960, there were used progestins, which are inducing a pseudo-pregnancy endometrial aspect or endometrial atrophy at microscopy [92]. The progestins are synthetic different derivates, such as C-21 progesterone derivates (medroxyprogesterone acetate, MPA, and depot MPA, and dydrogesterone,

(DYD- a semisyntethic progesterone derivate), or C-19 nortestosterone derivates (levonorgestrel, norethisterone, lynestrenol, desogestrel, and dienogest), or the 19-norprogesterone derivates without androgenic activity; nomegestrol acetate – (NOMAC) has a similar anti-gonadotropic activity compared to the 19-nortestosterone derivates with androgenic activity, norethisterone acetate (NETA) [93] and a separate class with drospirenone, the unique progestin [94]. The COCs with the synthetic ethinyl-estradiol (20, 30 μg/pill) plus one of the previously mentioned progestins represent a very important cathegory in the control of eutopic and ectopic endometria from intrinsic abnormal steroids signaling [95]. One must keep in mind the Japanese oppinion [96] that concurrent estrogen action is essential for maximal progestin effect in COC, fact controverted by some studies regarding patients satisfaction on pain alleviation in endometriosis, explained by summerizing endogenous estrogen local levels in ectopic endometrium to that of pills [97] but estrogen priming may be necessary to induce PR in endometriotic lesions [96, 98] as progesterone usually actions on estrogen primed tissue. Progesterone and progestins, alone or in association to a synthetic estrogen are considered first line therapy in endometriosis. The positive response to progestins alone or combined estrogen- progestins may induce only partial improvement, the ectopic sites are not eliminated or some patients do not respond at all [99] being recognized only the quiescence of lesions, at best [100] and when first line therapy fails – in one- third of women because progesterone resistance [79] or it is contraindicated, or it is not tolerated one recommends Gonadotropin-Releasing Hormone (GnRH) agonists, GnRH antagonists, and aromatase inhibitors being used in cases refractory to other therapy. Up to 2021 it was published a single RCT on COCs in endometriosis [101] as Donnez and Dolman [79] mentionned in the last European review. It is described a statistically significant, though modest, improvement in dysmenorrhea with OCPs given for four months compared to *placebo*, and a lack of any beneficial effect of OCPs on non-menstrual pelvic pain and dyspareunia, being appreciated the studies failure to report data on their efficacy according to lesion phenotype [102, 103].

Patients present variable responses to progesterone/progestins, according to their pharmakinetics, to their capacities to reacts to medication (genes, receptors for E2, P4), to metabolize progesterone/progestins connected to their levels of N-Acetyl transferases, associated to drug kinetics control by acetylating and converting active forms into inactive metabolites, to their cytochrome P450 3A (CYP3A) system- one of the most known pathway in steroid hormones metabolism,and P450 3A polymorphism is not precisely known in endometrial patgology [89].

4.1.1 "Old" hormone therapies still active in endometriosis

During the long time of progestins usage it was reported a good rate of patient adherence and satisfaction [104, 105]. There are few direct comparisons between different types of progestins in endometriosis clinical studies, with the scarce evidence suggesting that when given by the same route and the same regimen, the effectiveness may be similar [7]. By binding to PRs, progesterone/the synthetic compounds, administrated orally or by non conventional routes (vaginal [106], intrauterine [107]) induce inhibition of estrogen synthesis through down regulation of ERs [64] and of steroidogenic enzymes in endometrial stromal cells, either by up regulation of the oxidative 17β-HSD type 2, which transforms E2 to E1 [108], being triggered by retinoic acid [109] or by reduction of 17β-HSD type 1 expression, and activity, – as was proved specially for MPA, DYD, dienogest [108, 110] which induces the inhibition of aromatase expression with a low local estrogen production in immortalized human endometrial epithelial cells [111] with inhibition of eutopic and endometriotic cells proliferation, and reducing cells survival by apoptosis

induction [112] with limitation of local angiogenesis and neurogenesis (proved with the CD31- a neurovascularisation marker), and linking all these mechanisms, the attenuation of the immune-inflammatory response (proved to be more accentuated on new progestins as drospirenone by its effects on inflammatory cytokines - VEGF, and nerve growth factor) [113] so progesterone/progestins change the morphology of endometrium- ectopic and eutopic with reduction of lesion sizes, but with net differences in their response to these drugs, as experimental and clinical studies demonstrated [7, 114], stages III- IV are not responding. Longitudinal assessment of endometrial morphology has demonstrated that the histology aspects are changing in time: initially one registers secretory differentiation, and after several cycles through ERs down- regulation one registers atrophy with tubular glands, weak secretory vacuolation, and stroma low cellular density [115]. Usually one recommends a HT for long term duration, short term therapy being insufficient to obtain the wanted effects, even with dienogest, – which in a short term therapy demonstrated a high frequency of decidualisation and a tendency of inflammation reduction, but it was not able to induce differences comparable to non- treated cases in terms of necrosis, glandular atrophy and angiogenesis [116] (**Table 1**).

4.1.2 Timing progesterone/progestins for preventing progesterone attenuance and progesterone resistance in endometriosis

The discussion on administration of progesterone from early ages of reproductive period, just to permit P4 to stop endometriosis progression, inflammation, and angiogenesis, by maintainance of ERs, PRs normal ratios in epithelial glands and stroma, is supported by Li et al. study [114] at University of Illinois at Urbana-Champaign, (USA). Endometriosis was induced in two immunocompetent mice groups, differently maintained afterwards: one group with E2, and the second group with E2 and P4 subcutaneously, at every 4 days beginning at 4 days before lesion induction (pre- P4 treatment). The endometriosis-like islands were very quickly developed, with different numbers, aspects and sizes according to steroids administrated- after E2 alone there were yellow, more numerous, larger, with abundant blood vessels and extensive adhesions; after E2 plus P4 were white, smaller, non-vascular, with loose attachment. The microscopy (H&E, special biomarkers, IHC for ER, PR, their genes) have shown marked differences regarding mitotic activity (Ki-67 reduction), glandular secretion, endothelial cells and angiogenesis (CD31 increased when was added P4 before induced endometriosis). Another peculiar aspect in the treated group with E2 plus P4 are the inflammatory response changes - first an increase, and later a reduction of inflammatory cells, and changes of their type in endometriosis-like tissues, with similarities between groups in the first 16 days, and a dramatically changed aspect of inflammation after 24 days from induced endometriosis, such as suppressed production of pro-inflammatory cytokines, and infiltration of immune cells in ectopic sites. The authors debated the P_4 action to alleviate lesion outgrowth and to maintain ERα and PR expression

• P_4 restricts expansion of the ectopic lesions by inhibiting endometrial cell proliferation, and neovascularization
• P_4 suppresses E_2-dependent inflammatory responses in the ectopic lesions
• P4 maintaines ERα/PR-mediated signaling; their loss in the ectopic lesions leads to resistance to P_4 therapy if the treatment is postinduction of lesion

Table 1.
Progesterone alleviates endometriosis, induced in the peritoneal cavities of femele immunecompetent mouse, maintained with estrogen if administered before illness induction (from Li et al. [114]).

when P4 is administrated before lesion induction. The use of RT- qPCR permited the endometrial genes assessment in eutopic and ectopic endometria, showing a progressive down-regulation of miRNA expression corresponding to ESR1, PRs and PR-stromal targets *Hand2* and *Hoxa-10* with time of disease progression, and in contrast a gradually increase of ESR2 miRNA, parallel to increased expression of ESR1, PRs, and *HOXA 10* in ectopic lesions, while *Hand2* expression remained suppressed when P4 was administered before lesion induction (PreP4). The P4 inhibitory effect was not observerd when P4 was started at 4 days after endometriosis induction (Post-P4). The study results clearly indicate that the loss of PR-mediated signaling components is a major causal factor for the P_4 resistance existing in mice with endometriosis. The conclusion is that progesterone supplementation from early moments of disease, when PRs are still present can preserve steroid responsiveness and ameliorate E_2-dependent disease progression, but when at later stage, P4 supplementation has minimum effects, because of PRs absence. The hope is that if PRs women's loss is progressive after disease onset, the add of P4/progestins may action with the wanted effects.

4.1.3 Not all progestins are equal in restoring estrogen- progesterone balance in endometriosis. New trends-dienogest

If there were questions if progestins are all equaly capable of acting on endometriosis lesions to induce apoptosis, or to inhibit cell proliferation, adhesion, invasiveness, angiogenesis/neuroangiogenesis, and inflammation, actually one knows their different actions and effects, according to their biochemical structure, and cross effects on glucocorticoid, mineralocorticoid and androgen receptors [117]. In the last 20 years, starting with the Japanese experiments [118] on rats induced- endometriosis, the progestin dienogest (DNG) was much analyzed in Japon, USA, Europe (The European Clinical Study Program) [119] in order to avoid progesterone resistance or progesterone attenuance, by reducing estrogen deleterious effects on endometrium- normal, eutopic and ectopic increasing PRs expression and decreasing proinflammatory cytokines, and the necessity of "add back" therapy imposed by GhRh agonists [120, 121] as it will be further discussed. It was demonstrated that DNG 2 mg/day (once/day in Europe, and 1 mg twice/day in Japon) [120] after 24–52 weeks of administration reduces lesions size, [122] without changing bleeding pattern [123] and with a good score regarding chronic pelvic pains [120]. Because it was proved an *in vitro* dose-dependent inhibition of human endometrial stomal cells proliferation together with morphological and functional changes [124], an Italian clinical study on 20 cases of endometriosis [125] had evaluated doses of 20 mg/day effects, for 24 weeks, with no comparative study-group, and showed no clinically significant effects on hemostasis, haematologic parameters, thyroid and adrenal, liver functions, glucose and lipid metabolism, or electrolyte balance, with maintainance of mean high-density lipoprotein-3 cholesterol from the baseline.

The morphological studies reported inhibition of endometrial cells proliferation, by down-regulation of ESR2/ESR1 *ratio* [126] and aromatase expression [127] with local estrogen synthesis reduction, and the inhibition of human endometrial stomal cells proliferation, together with functional changes, as it is prolactin synthesis- a typical marker for decidualisation [124] and the association of increased apoptosis in endometriotic lesions [128]. DNG increases the PR-B/PR-A *ratio* in ovarian endometriosis [126] and down-regulates the expression of CYP19A1, and inflammatory, and neuroangiogenesis factors through PR- A and B- isoforms [129]. Some studies have revealed that DNG reverses some alterations of the immune system by increasing natural killer cells in the peritoneal fluid, and spleen, parallel to

the decrease of peritoneal fluid cellular content, and lower peritoneal macrophages synthesis of inflammatory cytokine IL-1β [118], and inhibits IL-1β release by the endometriotic epithelial cells [130].

4.1.4 Extended regimen of continuous combined hormonal contraceptives in endometriosis

The continuous regimen or extended cycle vs. cyclic use of combined hormonal contraceptives was first proposed by Loudon [131] in a family planning clinic from Ediburgh (UK) by skipping the tablet-free interval of 7 or 4 days. The innitial proposed non traditional regimen was with 84 active pill with etyhil estradiol 50 μg plus linestrenol 250 μg /day and 7 days free, and it obtained a great adherence in women suffering of endometriosis, according to suppression of withdrawal bleeding, and inducing atrophy in ectopic and eutopic endometrium, as it is recognized by *Cochrane Database Syst Rev*., 2014 [132]. The regimen was recommended with levonorgestrel – LNG (90 or 100 μg/day), drospirenone- DRS (3 mg/day) [133, 134] desogestrel (150 μg/day) [135], NETA (1000 μg/day) [136], and recently dienogest (2 mg/day) [137] as progestins, associated to 20 or 30 μg/day of ethinyl estradiol. The regimen of ethinyl estradiol 20 μg plus LNG 90 μg/day was reported for 364 days at Eastern Virginia Medical School, Norfolk (USA) [138] and in Italy during 6 months with ethinyl estradiol 20 μg plus LNG 100 μg/day [139], or during 3 to 6 months in Germany, Frankfurt University [140, 141], and recently the Italian prospective open label study [137] analyzed ethinyl estradiol 30 μg/day plus dienogest 2 mg/day in a continuous regimen vs. 21/7 to assess quality of life and sexual function in women with endometriosis. The pharmaceutical industry created some drugs combinating ethinyl estradiol 30 μg/LNG 150 mg/day for 84 days plus 7 days *placebo*, or the combination of ethinyl estradiol 30 μg/LNG 150 mg/day for 84 days plus ethinyl estradiol 10 μg/day for 10 days, or of ethinyl estradiol 20 μg/LNG 150 mg/day for 84 days plus ethinyl estradiol 10 μg/day for 10 days [142] after the concept called "tricycle regimen" or "tricycling", first named so in Sweden in 1993 very easy to be followed, and very well appreciated by users [135].

The literature describes some attempts to short free hormones interval for the reduction of hormone withdrawal symptoms, as pelvic pains, headaches [143] and this regimen used LNG, norethindrone (1 mg/day), desogestrel, and norgestimate with ethinyl estradiol 35 μg or less/day. All these attempts were followed by better results of pelvic pain control, but after a longer duration of administration (as after 6 months of norethindrone).

One must consider the tricycle regimen of contraceptives in adolescents suffering of menorrhagia, dysmenorrhea, or with family history of endometriosis, in order to reduce the concerns of a future progress of an eventually later diagnosed endometriosis, existing already findings on this cathegory of women, at the Department of Adolescent Medicine of the University of Pitsburg (USA), with a significant ovarian suppression, endometrial atrophy, no metabolic change, and adolescents safety [144]. At this study one must add a recent one [145] sustaining that women who used the new generation of COC or only progestins have lower circulatory inflammatory biomarkers [IL-6, sTNFR2 (soluble tumor necrosis factor α receptor 2), and in a lower degree C-reactive protein] similar to the effect of a higher number of lifetime ovulatory years. The presence of progesterone after ovulation, the new generation of COCs, and the effects of progestins can be the explanation for the benefits in reducing systemic inflammation; being considered that chronic inflammation reduces ovulation rate in premenopausal women, and ovulation and menstruation increase local inflammation.

There are recent reviews on the comparison of flexible/extended COCs to cyclic COC use in endometriosis, published in 2018 in USA (on dysmenorhheea, non- pelvic pains, dyspareunia [146]), or in Europe [147] and the systematic review (2019) of only 8 RTC published between 1934 and 2018 (of a total 743 studies) on dysmenorrheea [148] and in 2021 [79]. It is shown a statistically significant, though modest, improvement in dysmenorrhea - a reduction of 50% when COCs were given for four months compared to *placebo* [147] and a shorter duration of only 4 days of the pains, with conflicting results on interference with daily activity, pain severity, and pain reccurence [148].

4.1.5 Different routes of administration for progesterone/progestins to increase positive effects in alleviation progesterone attenuation/resistance and estrogen dominance

Since many years one discusses non conventional routes for drug administration in order to avoid the second liver passage, and to increase bioavailable active substance where is necessary. Vaginal route for progesterone and medicated intrauterine devices are most analyzed for their beneficial endometrial effects, without or with less systemic effects of progesterone/progestins.

4.1.5.1 Vaginal route for micronized progesterone

Natural Progesterone has far more anti- inflammatory properties, fewer side effects, is very versatile in how it can be used, and the micronization of P4 is very important, and the oral micronized progesterone capsules were re-directed to be used vaginally [149]. Micronized P4 has a more selective effect on PRs, and results in less interaction with androgenic and mineral-corticoid receptors compared with progestins.

The vaginal route for P4 was proposed since many years ago [150] but the new hypothesis regarding the higher endometrial P4 levels than that obtained after intravenous administration was presented by Cicinelli and de Ziegler [151]. This phenomenon of preferential uterine distribution after vaginal administration was named "first uterine pass effect" [38] or "uterine specificity of vaginal progesterone" [152]. The high uterine level of P4 vaginally administered is explained by various putative modes of transport including direct diffusion through tissue, intracervical aspiration, absorption into the venous or lymphatic circulatory systems and countercurrent vascular exchange with diffusion from utero-vaginal veins/lymphvessels to arteries. While the serum P4 concentration is often low or "subphysiological", endometrial effects show in most cases clear and complete secretory changes, or pseudodecidual aspects, or atrophy after long duration of therapy [153]. In USA at Brigham and Women's Hospital [154] one recommends vaginal gel, cream, or suppositories, in a higher dosage for endometriosis control than that for replacement therapy recommanded in menopause, such as 300 mg twice a day for minimum 3 months, then 300 mg at bed-time.

4.1.5.2 Medicated intrauterine systems to restore estrogen-progesterone balance

The direct application of progesterone or a progestin (usually LNG), or of a SPRM (ulipristal acetate was proposed) was another potential option to control estrogen dominance in eutopic endometrium, for avoidance irregular effects of systemic progestins, considering a consistent inhibition of ERs expression in eutopic endometrium [107, 155] with pain reduction, or to avoid pain relapse in

postoperative period, and a total patients' satisfaction when compared to their attention for daily pills intake [156].

4.2 New therapeutic strategies to restore estrogen-progesterone endometrial balance in endometriosis. Selective estrogen receptor modulators (SERMs). Selective progesterone receptor modulators (SPRMs)

Medical literature presents under the name of selective estrogen receptors modulators (SERMs) a relative new cathegory of drugs aimed to target down-regulation of E2 signaling, by a direct binding to ERs in a tissue specific manner [91]. The studies on rat induced endometriosis [157] have shown the reduction of endometriotic lesions by down-regulation of ESR1 and cell proliferation by bazedoxifene or by raloxifene, but in a RCT on administration of raloxifene (180 mg/day) after laparoscopically apparent complete excision of ectopic lesions, it was recorded a shortly time for chronic pain relapse with raloxifene vs. *placebo*, but without recurrence of endometriotic lesions at the second laparoscopy [158] and these results have reduced the enthusiasm for first and second generation of SERMs in endometriosis. The third generation of SERMs administration - basedeoxifene, reduced glands size and number of ectopic sites in mice [159].

The selective progesterone receptor modulators (SPRMs) are known since long time, with the antiprogesterone representative RU 436 or mifepristone. SPRMs were proposed to treat unresponsive cases to progestin treatment, due to progesterone resistance dilemma [160] connected to their direct interaction to progesterone receptors, in order to reduce estrogen- induced cells proliferation and prostaglandins production [161]. Two old multicentres trials on mifepristone showed its efficacy in the endometriosis chronic pain control, with lesions size reduction, although results are mixed [162, 163].

Ulipristal acetate suppressed ectopic endometrium induced in mice, with slow reappearance after discontinuation [100]. After many discussions on the promising evidence of inhibiting human endometrial cell proliferation *in vivo* [164] and on the so-called progesterone receptor modulator-associated endometrial changes (PAEC) recorded after 6 months of therapy, which is reversible after ulipristal discontinuation [164] the liver life threatening complications induced the discontinuation of the study on endometriosis effects [165].

Per global these so called "new" classes of molecules with selective receptors of steroid hormones modulation objectives did not covered the expections in endometriosis, according to women pathologic condition progressively induced on their steroid hormones receptors dysregulation/loss.

4.3 New potential therapeutic perspectives: A combination therapy using agonist of ERβ and the SRC-1 isoform as the next generation of endometriosis therapy to restore estrogen-progesterone signaling balance

Long duration of systemic hypoestrogenism may affect brain, heart, and bones, in young women, and for non responders to first line therapy mentionned above, long term medication with GnRH agonists/ antagonists or aromatase inhibitors cannot be recommended, fact that imposed more researches to try to improve estrogen dominance/progesterone resistance, to stop ectopic tissue growth and disease stage progression with chronic pelvic pains, and infertility. These aims were objectives at the Bayllor College of Medicine, Houston (USA) where it was proposed a combination therapy using an agonist of ER β and the steroid receptor coactivator-1 (SRC 1) isoform as the next generation of endometriosis therapy – Han et al. [44] (**Figure 2**).

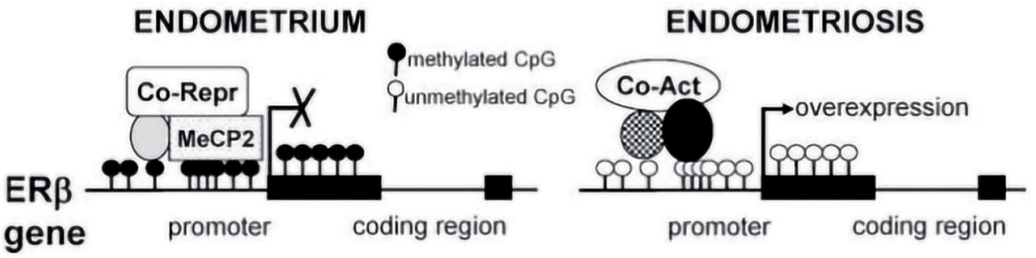

Figure 2.
Hypothesis of Bulun SE, et al. on hypomethylation of ERβ promoter in endometriotic stromal cells vs. hypermethylation, which suppresses the promoter expression in normal endometrium by blocking transcriptional complex including co-activators of ER- β (adapted from Bulun et al. [45]: open acces).

The combination of ERβ- selective agonist and SRC-1 is based on the significant supressive effect of PHTPP on ectopic lesion growth by inhibiting ERβ activity in mice induced endometriosis [166] associated to minimum side effects on ERα, without influences on eutopic endometrium or negative influences on mice fertility. SRC-1 is considered a PR co-activator, and indirectly through it, ERβ may impair PR-mediated signaling in the ectopic lesions, because actually it is no evidence available to show that PR could potentially interact directly with ERβ [167]. These drivers combination allows marked suppression of ectopic lesion growth compared with either individual agents alone, both demonstrating essential roles in early stages of disease pathogenesis [168] specially on apoptosis modulation and inflammation reduction.

4.4 Potential therapeutic options for estrogen dominance control

Several medical treatments for endometriosis directly aim to reduce E2 production or action in order to mitigate E2 dominant conditions, and actually one discusses GhRh agonists, and the new class of GhRh antagonists. These therapies are efficient in cases wishing to conceive, and for the control of chronic pelvic pains- menstrual and non-menstrual [169] but associated hypoestrogenism is cause of many health concerns, requiring hormone "add-back" for long term use [91]. Numerous studies included in the *Cochrane Data Base Systematic Review* (2003) [170] revealed since long time that these effects limit the duration of treatment, which cannot be administered without "add back"/hormone-replacement therapy [171] and treatment cannot be dose-adjusted to alleviate the side effects - Practice Committee of the American Society for Reproductive Medicine (2014) [172].

The recent history of HT for estrogen dominance and progesterone resistance in endometriosis shows that the "old" injectable depot MPA, which can decrease ESR1 and ESR2 while increasing PR-A and PR-B in the eutopic and ectopic endometria [173] has equivalent efficacy to leuprolide- a GnRH agonist, in reducing pain, but with less adverse hypoestrogenic effects on bone density [174].

4.4.1 GnRH agonists. GnRH antagonists

Injectable GnRH agonists (leuprolide, diferelin, nafarelin) are normally second-line treatments. Which decrease hormone levels by down-regulating the pituitary through negative feedback mechanisms [91] and indirectly they favor an endometrial complete silenced hormonal milieu, on the bases of estrogen dominance concept. GnRH agonists have been shown to be effective in reducing endometriosis-related pain [175] with adverse effects – hot flushes, bone mineral density loss, or coronary heart disease, headaches due to a hypoestrogenic state, requiring hormone

"add-back" [91]. It was reported a mean percent decrease from baseline in bone mineral density at the lumbar spine of 3.2% at 6 months, and of 6.3% at 12 months after leuprolide alone, and these side effects were associated with rates of discontinuation by 6% because hot flushed, and 8% because of emotional changes [171].

GnRH antagonists, known since long time [176] were in last 10 years under investigation for endometriosis treatment in USA, and Europe according to their capacity to downregulate gonadotropins, without flare-ups like GnRH agonists because they rapidly and directly compete for GnRH receptors [177] and the oral administration is another benefit. Their mechanism of action is different to that of GnRH agonists. After an initial stimulatory phase desensitize GnRH receptors in the pituitary, causing a subsequently depletion of pituitary gonadotropins and full suppression of E2 to levels that are equivalent to those associated with bilateral oophorectomy [178].

Based on Barbieri RL (1992)" estrogen threshold hypothesis" [179] the 2 large multicenters RCTs (Australia, Brazil, Canada, New Zeeland, Poland, USA) [177] have concluded that the new oral Elagolix, a nonpeptide GnRH antagonist, in 2 different doses (one with Elagolix 150 mg/day, and the other RCT with Elagolix 100 mg twice/day) significantly lower scores for dysmenorrhea and non-menstrual pelvic pain than *placebo* after 3 and respectively 6 months of treatment, and dyspareunia at 3 months, with significantly better results in cases on 200 mg/day with respect to the use of rescue analgesic agents at 3 months and 6 months, dyspareunia at 3 months, and rescue opioid use at 3 months less than did those receiving *placebo*. The dysmenorrhea control was better than that of non-menstrual pelvic pains, dysmenorrhea is mostly dependent on cyclic changes in ovarian hormones, whereas the mechanism of non-menstrual pelvic pain are considered more complex [180]. The results allowed the researchers to consider that complete estrogen supression may not be needed to controll endometriosis- associated pain, and estrogen may be adjusted to a level that is adequate to control pain with minimum hypoestrogenic effects (hot flushes, bone mineral density, lipid levels), more frequently claimed in the higher dosage, similar to those induced by GnRH agonists. Elagolix was associated with an antiproliferative effect at each dose, and with endometrial atrophy at higher dose, which was consistent with decreases in endometrial thickness at that dose, but there were considered some limits of the study, as time since endometriosis first surgical diagnosis (in between 10 years), short duration (6 months) of drugs administration. Elagolix did not completely suppress ovulation at either of the two doses [181] being recorded pregnancies, even if patients were recommended to use non – hormonal contraceptive methods during trials. Presently one waits the published results of a phase 3 multicenters RCT in Eastern European countries on an daily oral combination of GnRH antagonist (relugolix) with low doses of estradiol and norethindrone acetate regarding endometrial histology, and endometriosis associated chronic pain, and side effects in comparison to the 4 weeks injectable leuprolide.

4.4.2 Aromatase inhibitors

Aromatase inhibitors (AI), anastrozole and letrozole - the most known derivates, were destinated for control of local E2 levels in many pathologies, and in endometriosis they induce regression of peritoneal lesion size, in a higher degree than MPA [182] by reducing androgen aromatization into estrogens, both in adipose tissue and within endometriotic sites. These drugs are inhibiting endometrial progenitor cells migration to ectopic sites [183], and by increasing apoptosis, and diminishing endometrial VEGF and PGE2 in a mouse model [184] they reduce chronic pelvic pains. AI have significant adverse effects like irregular bleeding, and joint pains [185].

AI action is explained by the promotion of pituitary gonadotropin hormones release, with consequent ovarian stimulation; therefore, they must be combined with a progestin or other method of gonadotropin inhibition to treat endometriosis in premenopausal women [186]. There was compared the association of letrozole (2,5 mg/day) to NETA (2,5 mg/day) vs. NETA (2,5 mg/day) alone, and the Italian open-label study proved a better control for pain and dyspareunia of the drugs association in rectovaginal endometriosis [187] with a better sizes reduction of rectovaginal nodules [188] and of endometrotic ovarian cysts [189]. The effect of the combination of a progestin to an AI is not lasting after termination of HT, so Reis et al. [7] in their published review on progesterone ligands consider letrozole as a second therapeutic- line for selected patients, who fail to respond to first line HT- progesterone/progestins.

5. Potential therapeutic perspectives to restore the estrogen-progesterone receptors balance in endometriosis

The dysregulation of ER and PR in endometrial glandular epithelium and stroma is for sure a pathological mechanism involved in eutopic and ectopic endometrium in women suffering of endometriosis, a disease with onset during embryo-fetal life, and long time duration, sometimes up to death. The prevention and the attemps to maintain or restore the ERα/ERβ, and PR-A/PR-B through their normal genes is one of new potential contemporary therapeutic options.

5.1 Genetic/epigenetic interventions in dysregulated endometrial progesterone responses in endometriosis

Progesterone resistance in endometriosis has genetic causes as PRs gene polymorphisms, altered microRNA expression, and epigenetic changes of PRs and their targets. A consequence of impaired progesterone action is that hormonal therapy is rendered ineffective for a subset of women with endometriosis. Environmental toxins as dioxin may play a role in the genesis of endometriosis by permitting an inflammatory milieu.

5.1.1 Progesterone responsive genes methylation: a cause of a dysregulated progesterone response

The studies at Yale University, New Haven, Connecticut (USA) using RT-qPCR for assessment of endometrial genes in mice induced endometriosis compared to normal mice [190] have demonstrated the silencing or inhibition of P4 target HOX genes (HOXA 10/HOXA 11, known also as genes of receptivity) by promoter hypermethylation - an epigenetic mechanism, which favorizes lack of menstrual cycle variation of PRs distribution, which is proper in normal menstruated women, and this is appreciated as a partial explanation for the refractoriness of some endometriotic lesions to progesterone/progestin therapy [7, 191]. Altered PRs expression or diminished activity may lead to attenuated or dysregulated P4 response in ectopic endometrium, and decreased expression of P4 responsive genes including *HOX genes* in the eutopic endometrium. Cakmak and Taylor [191] and Lee et al. [190] concluded that normal endometrium placed in an ectopic location, in order to create experimental endometriosis led to characteristic changes in gene expression of eutopic endometrium, fact that was previously observed regrading stromal stem cells migration to ectopic sites, without this genetic/epigenetic explanation, and it was controverted. These data were suggestive for the existence of a signal

conduction pathway from endometriosis that alters endometrial gene expression through altered *Pgr* signaling and epigenetic programming. The relatively permanent nature of methylation may explain the widespread failure of HT [7]. One discusses about promoters methylation, being controversies if both PRs promoters are methylated, discovering only PR-B methylation, not PR-A [39] or both PRs promoters [192] or DNA methylation of the CG- islands in *PR* promoter, and its gene *HOXA 10* [114] as there are controversions regarding ERs genes (*ESR-1* and *ESR-2*), being hypomethylated CpG island at the *ESR2* promoter region,- involved in primary mechanism responsible for differential expression of *ESR2*, discovered to be increased in ectopic and eutopic endometria [40] while other study from Brazil [192] denies their methylation in eutopic and ectopic endometria.

5.1.2 DNA methylation inhibitor: a new therapeutic perspective/challenge to restore PR-mediated signaling molecules in endometriosis

The women's ectopic and eutopic endometrial progressive loss of PRs and ERα/PR-mediated signaling in the developing ectopic lesions during 7 to 12 years from histologic disease's onset to clinical symptoms/signs permits to health care providers to intervene in the epigenetic regulation therapeutic control.

The animal studies at the University of Illinois at Urbana-Champaign (USA) [114] have shown that a DNA methyltransferase (DNMT) inhibitor, such as Decitabine (DAC, 5-aza-2′-deoxycytidine), an analogue of deoxycytidine that can incorporate into DNA strands and cause DNA demethylation [193] compared to vehicle administration in immunocompetent mice induced endometriosis, treated also with E2 had alleviated lesion growth, and increased expressions of PR protein, and miRNA corresponding to *Esr1*, *Pgr*, *Hand2*, and *Hoxa10*, (P4 target), but not for *Ccl5* and *Ptgs2* in the eutopic endometrium and ectopic sites. The results of the study enable the authors to review the involvement of estrogens and progesterone in eutopic and ectopic endometrium, the epigenetic regulation including DNA methylation, the fact that ERα and ERβ *(*ESR1 and ESR2), PRs (PRA and B), as well as PR-targets *Hoxa10*, *Gata2/6*, and *Hand2* are susceptible to DNA methyltransferases, leading to an aberrant expression of these molecules in endometriosis.

Early studies showed that the promoter sequences of ERα and ERβ (*(*ESR1 and ESR2), PRs (PR-A and B), as well as PR-targets *Hoxa10*, *Gata2/6*, and *Hand2* are susceptible to DNA methyl transferases, leading to an aberrant expression of these molecules in endometrial diseases [194] and loss of PR-mediated signaling during disease progression contributes to the increased susceptibility to P_4 resistance in ill women. Li et al. [114] accepted the proposed role of inflammation to provoke widespread changes in the genes and chromatin landscape of lesions, because their analyses showed that DNA methylation in PRs and *Hoxa10* promoters was enhanced in the ectopic lesions in comparison to the normal endometrium, and inhibition of genome-wide DNA methylation in female mice restrained lesion expansion and partially restored target gene expression.

6. Conclusions

Endometriosis is a chronic disease, with possible onset in embryonic life, latency in childehood, reactivation from the menarche, with clinical symptoms and signs difficult to be early accurate assessed during reproductive years. Endometriosis has a progressive evolution, which drives through tissue intrinsic properties to increase lesions size and number, and to functional damages of original eutopic endometrium. The cascade of dysregulations in chromatin machinery is difficult

to be stopped by hormone therapy and surgery (associated in different strategies), when the abnormal signaling of steroid hormones has started: endometrial estrogen dominance and progesterone attenuate response up to progesterone resistance, because their genes epigenetic disorders. The 7–12 years delay in diagnosis and proper therapy drives to accentuation of chronic pelvic pains, dyspareunia, dyschezia, infertility/subfertility.

The best therapy is to avoid the dysregulation of steroid hormones signaling, induced initially in ectopic and later in eutopic endometrial stroma and glands, to maintain or to restore the estrogen/progesterone receptors natural balance, which may be possible when an early intervention, from the menarche. One may discuss about timing in starting HT in adolescent girls with family history of endometriosis, precocious dysmenorrheal, menorrhagia, abundant blood and clots loss, favorising menstrual blood reflux.

First line therapy is progesterone/progestins, working in prevention of estrogen dominance and progesterone dysregulated signals, and can maintain their positive effects, when it is early administrated, as animal models have shown. One must recommend this first line therapy, for a long time duration, with a single drug (micronized progesterone, or dienogest, a new progestin) or combined with a synthetic/natural estrogen in COCs, in cyclic or in continuous/extended regimens up to response failure, with the advice to avoid drug discontinuation. Vaginal route for micronized progesterone, IUD with progesterone/levonorgestrel may work better for alleviation of estrogen dominance and progesterone resistance.

GnRH agonists/antagonists- second line therapy, are active in correcting the steroid imbalance, but less than our expectances, even with the new oral molecules (as elagolix), or combination of molecules [GnRH antagonists (relugolix or elagolix) plus an estrogen, or plus an estrogen and a progestin], which were proposed to avoid or to reduce add back therapy. The most recent studied molecule of elagolix may be used no longer than 24 months, because a longer administration may impose add back therapy.

Aromatase inhibitors are also second line therapy, recommended in selected patients for refractory endometriosis, with chronic pelvic pains. Letrozole combination to norethindrone acetate is better than the progestin alone in correcting estrogen dominance, and progesterone resistance.

The new therapeutic perspectives regarding the combination of ER agonists with co-activators, and DNA methylation inhibitors are still in studies at high level technology laboratories, not for current medical use.

Conflict of interest

None.

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