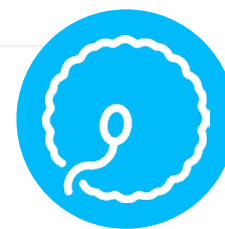


Progesterone Resistance in Endometriosis



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Abstract

Endometriosis is characterised by the presence of endometrium-like tissue on the pelvis and other organs. Progesterone resistance due to suppressed progesterone receptor (PGR) expression and action is a general feature of endometriosis and is a cause of endometriosis-associated chronic pelvic pain, infertility, inflammatory disorders, and cancer. It appears that progesterone receptor polymorphisms may not be associated with the susceptibility to endometriosis. On the other hand, PGR expression and activity in target cells is significantly dysregulated in both eutopic and ectopic tissues compared with control endometrium. However, the underlying epigenetic mechanisms for PGR suppression in the eutopic tissue are different from ectopic tissue. The aim of this paper was to present an overview of different aspects of progesterone resistance and its application in endometriosis. Finally, this article also presents a few important, unmet questions related to the failure of progesterone treatment in alleviating clinical conditions in endometriosis.

Key Points

1. Endometriosis affects nearly 10% of females of reproductive age; progestin treatment fails in a large number of these patients, likely due to progesterone resistance.
2. Progesterone resistance may be due to suppressed progesterone receptor expression and action and is a cause of endometriosis-associated chronic pelvic pain, infertility, inflammatory disorders, and cancer.
3. There is an urgent need for deeper understanding of the cellular and molecular mechanisms of progesterone resistance in endometriosis, for both ectopic and eutopic tissues, to underpin novel approaches to treatment.

INTRODUCTION

Growth of endometrial tissue outside the uterus, frequently but not exclusively, in the pelvic structures gives rise to endometriotic lesions in the peritoneum (peritoneal endometriosis), the ovary (ovarian endometriosis or endometrioma), and the deep pelvis (deep infiltrating endometriosis), and infrequently in the distant organs.¹ According to Sampson's theory, deposits of viable endometrial cells following their reflux into the peritoneal space via the fallopian tubes during menstruation may adhere and grow, and give rise to endometriosis.² In an elegant review, Redwine³ challenged this theory and demonstrated, by analysing a large number of parameters, that endometriosis tissue is primarily reflected dissimilarity than similarity with eutopic endometrium in the uterus, including inadequate secretory differentiation in endometriotic cells under progesterone dominance during the luteal phase.

Nisolle and Donnez⁴ speculated that inadequate secretory maturation in the endometriosis might cause from the reduction in progesterone receptor (PGR). Zeitoun et al.⁵ and Attia et al.⁶ observed that 17- β -hydroxysteroid dehydrogenase type 2 (17 β -HSD2), the activity of which transforms oestradiol to less potent oestrogen (oestrone) and is stimulated by progesterone in endometrial glands, was significantly reduced in endometriotic tissue during the luteal phase, along with markedly repressed levels of immunoprecipitable PGR throughout the menstrual cycle.

The fact that progestin treatment fails to regress endometriosis in three out of 10 females is also indicative of inadequate machinery of progesterone action in the endometriotic tissue.^{7,8} These observations were suggestive of the absence of certain responses to progesterone action.

Taking these observations together, a theory of 'progesterone resistance' as the mediator of pathogenesis of endometriosis was forwarded in the 2000s. Since then, though more intensely in the last decade, the theory has been under scrutiny.⁸⁻¹² An overview of this theory and its application in explaining the pathogenesis of endometriosis and its management will be presented in this paper.

PROGESTERONE RECEPTOR

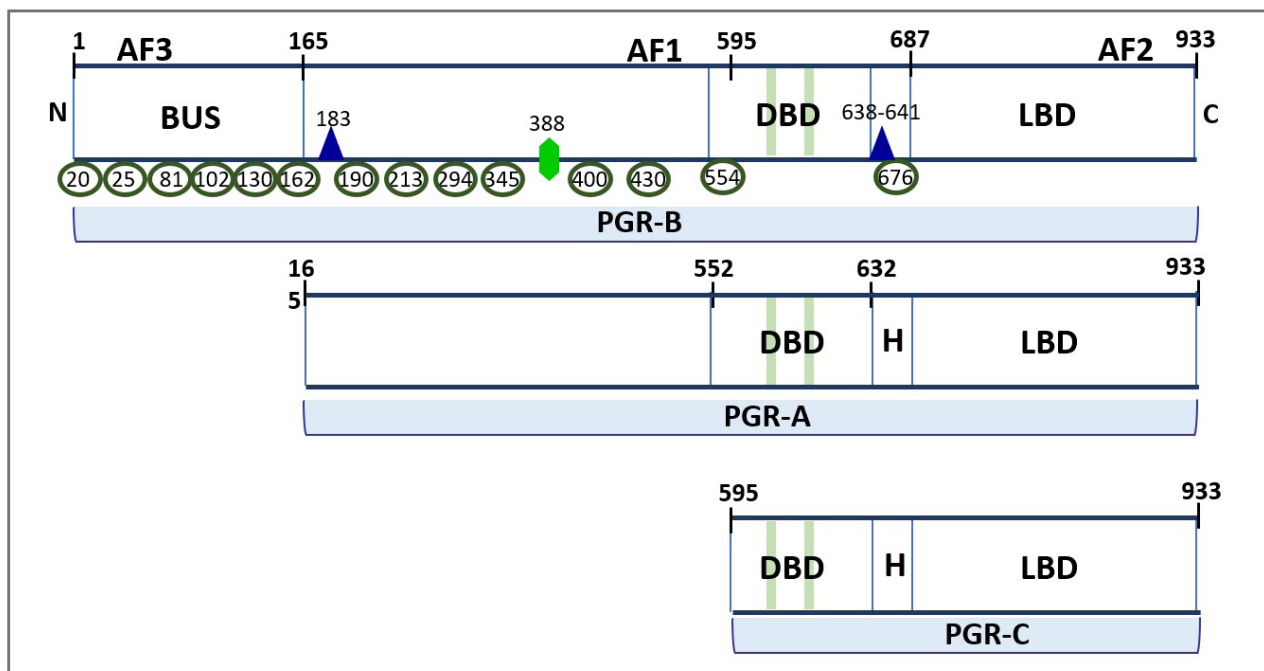
Progesterone is a steroid hormone primarily synthesised by the ovaries and adrenal glands, and also by the placenta during pregnancy. Progesterone, although quintessentially the 'pregnancy hormone', also plays an important role in several non-reproductive tissues such as the breast, heart and vascular system, brain, and bones.¹³ The physiological actions of progesterone in target cells are mediated by its binding to PGRs: classical and non-classical. Typically, classical PGR regulates the expression of progesterone responding genes, which result in slowly emerging, long lasting cellular responses. On the other hand, progesterone binding to non-classical PGR activates secondary messengers and signal transduction pathways and mediates rapid responses. A detailed discussion on the physiology of different types of PGR is beyond the scope of the present paper; however, the authors present a synopsis on the topic in the following section. Interested readers may be referred to the comprehensive review articles that covered different aspects of PGR in mammalian cells and specifically in endometrium.^{11,14-19}

Classical Progesterone Receptors

There are two main isoforms of classical PGR: PGR-A (94 kDa) and PGR-B (120 kDa). Both are transcribed from the same gene, but by two different promoters. As schematically presented in [Figures 1 and 2](#), these two isoforms are very similar except that PGR-A lacks 164 amino acids that are present at the N-terminus of PGR-B. Unbound PGR in cytoplasm are complexed with chaperone proteins.¹⁴⁻¹⁹ Several lines of evidence suggests that PGR-A is functionally distinct from PGR-B, and thus tissue-specific distribution patterns of PGR-A and PGR-B result in the observed diversity of progesterone-mediated actions.

Generally, PGR-B is the positive regulator of the effects of progesterone, while PGR-A serve to antagonise the effects of PGR-B.¹⁴ When progesterone binds to the ligand-binding domain of PGR, the receptor initiates a series of conformational changes, and it is released from the chaperone proteins to finally enter into the nucleus. In the nucleus, PGR dimerises to form homodimers (AA, BB) or heterodimers

Figure 1: Three isoforms of classical progesterone receptors.



PGR-B (120 kDa), but not PGR-A (94 kDa), includes 164 additional amino acids in the NTD (shown as BUS), where the AF3 domain and multiple phosphorylation sites are located. The NTD also contains an activation factor domain (AF1), which is common for PGR-B and PGR-A. The protein tertiary structure results in a folding at the H region between the DBD and LBD. The green bars in the DBD represent zinc-finger motifs. Post-translational phosphorylation (shown as green ellipses), acetylation (shown as violet triangle), and SUMOylation (shown as green hexagon) can occur basally or in response to ligand binding and affect PGR transcriptional activity. The numbering reflects amino acid residue positions.

AF1: first activation factor; AF2: second activation factor; AF3: third activation factor; BUS: B-upstream segment; DBD: DNA-binding domain; LBD: ligand-binding domain; NTD: N-terminal domain; PGR: progesterone receptor.

(AB), and binds to the progesterone response element sequence in the target gene.¹⁴⁻¹⁹ A third variant of PGR, PGR-C isoform (60 kDa), has also been described in humans (Figures 1 and 2). PGR-C also can form heterodimers with PGR-A and PGR-B and regulates their transcriptional activity.²⁰ Such diverse possibilities of dimerisation of PGR potentially gives rise to a wide variety of physiological responses. The binding of PGR dimer to progesterone response elements follows their recruitment to coregulators (coactivators or corepressors) and regulation of the subsequent PGR-mediated target gene expression in an isoform-specific manner.^{14,19}

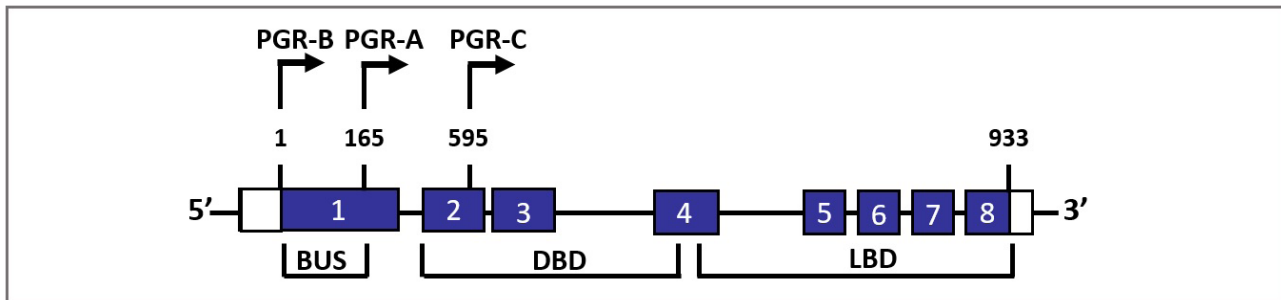
Figure 3 shows a schema of canonical mechanism of PGR action. PGR isoforms interact with one another and mutually regulate their

own activity. For example, PGR-A inhibits PGR-B action by its inhibitory domain and, thereby, PGR-A decreases the effects of progesterone on its target cells.^{14,19} Additionally, tissue-specific coregulator expression along with subnuclear localisation of PGR and coregulator association may mediate tissue-specific progesterone action.^{14,19,23}

Non-classical Progesterone Receptors

Non-classical PGRs are usually located on the cell surface as single transmembrane receptors. These receptors belong to G protein-coupled receptor superfamily and are associated with tyrosine kinase activity. Non-classical PGRs are of two types: membrane progestin receptors (mPR) family, also named the progestin and adipoQ receptor (PAQR), and the progesterone

Figure 2: Schematic representation of genomic configuration of three classical progesterone receptor isoforms and splice variants.



The nuclear PGR gene is composed of eight exons with 3100-bp coding regions and 5'- and 3'-untranslated regions. PGR-B and PGR-A isoforms are transcribed from two alternate transcription initiation sites and are identical to amino acids 165–993. PGR-C (60 kDa) isoform results from an in-frame initiation of translation and lacks exon 1.

BUS: B-upstream segment; DBD: DNA-binding domain; LBD: ligand-binding domain; PGR: progesterone receptor.

receptor membrane component (PGRMC) family, both having several subtypes.^{8,11,16,19,24} There is evidence to suggest that both types of non-classical PGRs may interact to mediate their actions in target cells. The physiological significance of non-classical PGRs in the uterus is not clear. However, as discussed in the following section, these receptors are associated with the menstrual phase specific functions of uterine cells.⁸

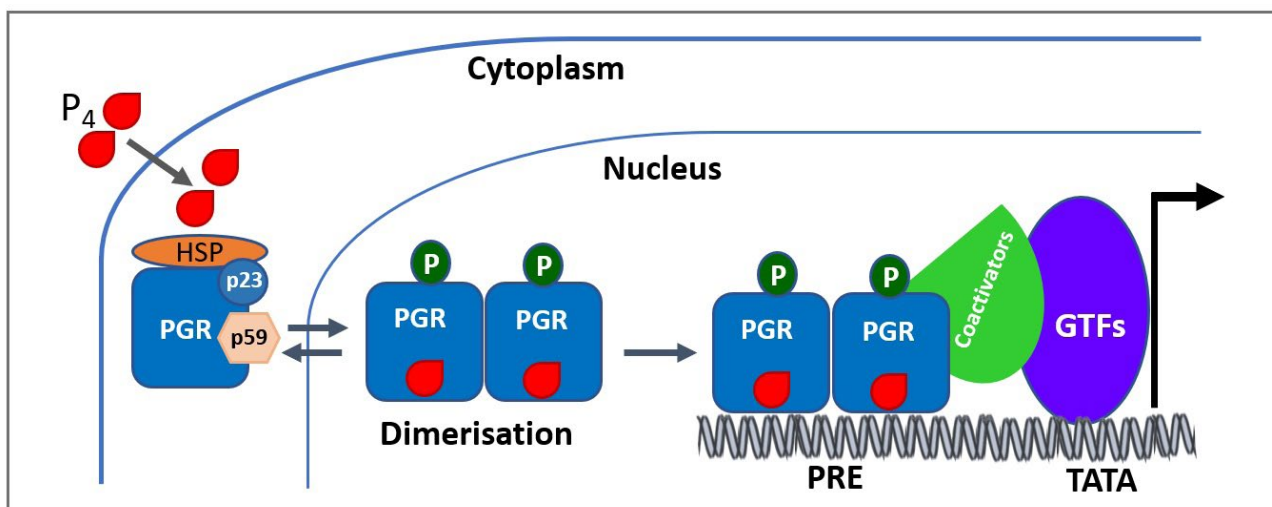
Progesterone Receptors in Endometrium

Both classical and non-classical PGRs exhibit differential expression depending on endometrial cell type, and the phase of the menstrual cycle (Figure 4). Both PGR-A and PGR-B are expressed in the endometrial epithelium during early to mid-luteal phase, seemingly in preparation of embryo implantation.^{18,19} The inhibitory effect of PGR-A on the expression of PGR-B causes negative regulation of the action of PGR-B, and thereby promotes hyperplasia and inflammation in this tissue.^{18,19} During implantation, however, the expression level of PGR-A drops, while that of PGR-B remains constant to support the secretory function of glands of endometrium *functionalis*. On the other hand, PGR-A is the dominant isoform in endometrial stromal cells throughout the luteal phase and provides support to decidualisation,

which is integral to the implantation process.¹⁶⁻¹⁹ In fact, very low expression of both isoforms in endometrial cells may result in unexplained infertility and implantation failure. PGR knockout experiments in mouse studies demonstrated that the expression of PGR-A, but not of PGR-B, is obligatory for successful implantation and establishment of pregnancy.²⁵ On the other hand, the overexpression of PGR-A results in uterine enlargement and endometrial hyperplasia.^{8,10,18} Thus, the ratio of PGR-A-to-PGR-B appears critical for the normal response of endometrium to progesterone.²⁶

Among non-classical PGRs in humans, transcript levels of PGRMCs, mPR α , mPR γ , and mPR ϵ fluctuate depending on the menstrual cycle phase. For example, levels of messenger RNAs (mRNA) for PGRMC1, mPR γ , and mPR ϵ are upregulated during the proliferative phase and progressively decrease during the secretory phase, whereas mRNAs for mPR α and PGRMC2 are higher in the secretory phase along the increasing levels of luteal progesterone.^{8,16,19,24} On the other hand, the levels of mPR β , which are relatively higher in the human endometrium than that of mPR α , do not change significantly during the menstrual cycle; however, its expression is critical on Days 10–14 of the human menstrual cycle, as revealed in patients with a history of recurrent spontaneous abortion.^{16,19}

Figure 3: A simplified scheme of the mechanism of progesterone receptor activation.



Ligand-free PGRs are present as inactive complexes associated with HSPs and chaperone proteins (p23 and p59). When progestin binds to the PGR, it undergoes conformational changes along with dissociation of HSPs and chaperone proteins (p23 and p59). PGRs then undergo dimerisation and bind to the HRE in the target DNA. Ligand-dependent conformational changes allow for the recruitment of cofactors and other GTFs to the promoter, producing a transcriptionally active complex that can direct gene transcription.

Adapted from Mani S, Portillo W.²¹ and Hill KK et al.²²

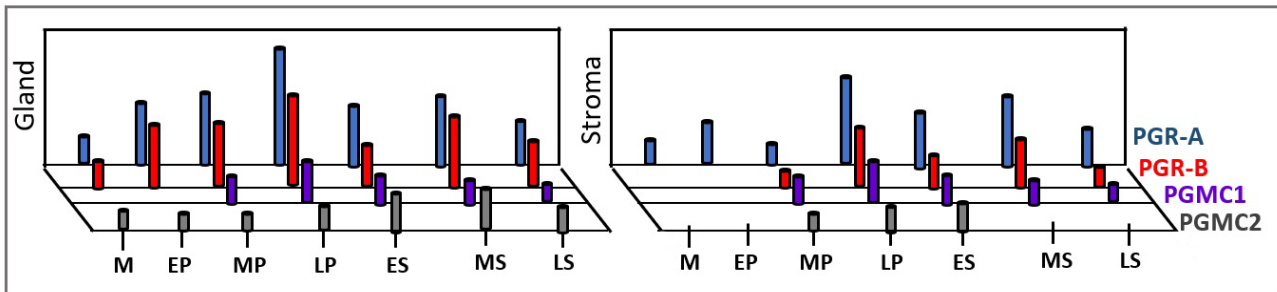
GTF: general transcription factors; HRE: hormone response element; HSP: heat shock protein; P₄: progesterone; PGR: progesterone receptor; PRE: progesterone response element.

As seen in Figure 4, PGRMC1 and PGRMC2 show inverse expression patterns during the menstrual cycle. PGRMC1 displays regulatory action on PGRMC2. PGRMC1 is involved in cell proliferation in the endometrium during the proliferative phase of the menstrual cycle.^{16,19} On the other hand, PGRMC2 inhibits cell proliferation and supports endometrial differentiation during the secretory phase of the menstrual cycle.^{16,19,24} Thus, the reported inverse profiles of PGRMC1 and PGRMC2 in the glandular and stromal compartments of human endometrium during the menstrual cycle appears important for endometrial growth and maturation. Several lines of evidence indeed indicate that both PGRMC1 and PGRMC2, and their expression ratio in endometrial epithelial and stromal components, are critical for endometrial preparation for successful pregnancy.^{16,24}

PHYSIOLOGICAL BASIS OF PROGESTERONE RESISTANCE

In a case report, Keller et al.²⁷ reported on a 23-year-old female with initial complaint of infertility, who demonstrated inadequate endometrial maturation during luteal phase consistent with inadequate corpus luteum syndrome; however, she had a normal serum pattern of progesterone, oestradiol, follicle-stimulating hormone, luteinising hormone, and their cytosol-binding proteins. Exogenous progesterone did not correct the abnormality. Further investigation revealed inadequate maturation of her endometrium that caused from a markedly reduced number PGR in the target cells.²⁷ Thus, it appeared that the condition of 'pseudocorpus luteum insufficiency' could have occurred due to progesterone resistance at the receptor level in the target cells of endometrium.²⁸ Similar defect had been reported in a subgroup of females with infertility.²⁹

Figure 4: Expression pattern of classical progesterone receptor-A and progesterone receptor-B and membrane receptors progesterone receptor membrane component 1 and progesterone receptor membrane component 2 in glandular (shown as "Gland") and stromal compartment (shown as "Stroma") of human endometrium in a typical menstrual cycle.



Marked expression of PGR-A and PGR-B in the LP and at MS is notable. PGRMC1 and PGRMC2 show subtle differential expression patterns during the menstrual cycle.

Adapted from Reis FM et al.⁸

EP: early proliferative phase; ES: early secretory phase; LP: late proliferative phase; LS: late secretory phase; M: menstrual phase; MP: mid-proliferative phase; MS: mid-secretory phase; PGR: progesterone receptor; PGRMC: progesterone receptor membrane component.

Gene polymorphisms and epigenetic modifications to PGR may, theoretically, cause such progesterone resistance. Furthermore, anomalies in down-stream signalling elements, target genes, and regulator modules that are directly and indirectly linked to progesterone actions may cause functional progesterone resistance. Both types of progesterone resistance may be constitutively present in the target tissue or may be acquired by the target cells.^{9,10,30,31} In the following sections, the authors discuss how both types of progesterone resistance are associated with endometriosis.

PROGESTERONE RESISTANCE IN ENDOMETRIOSIS

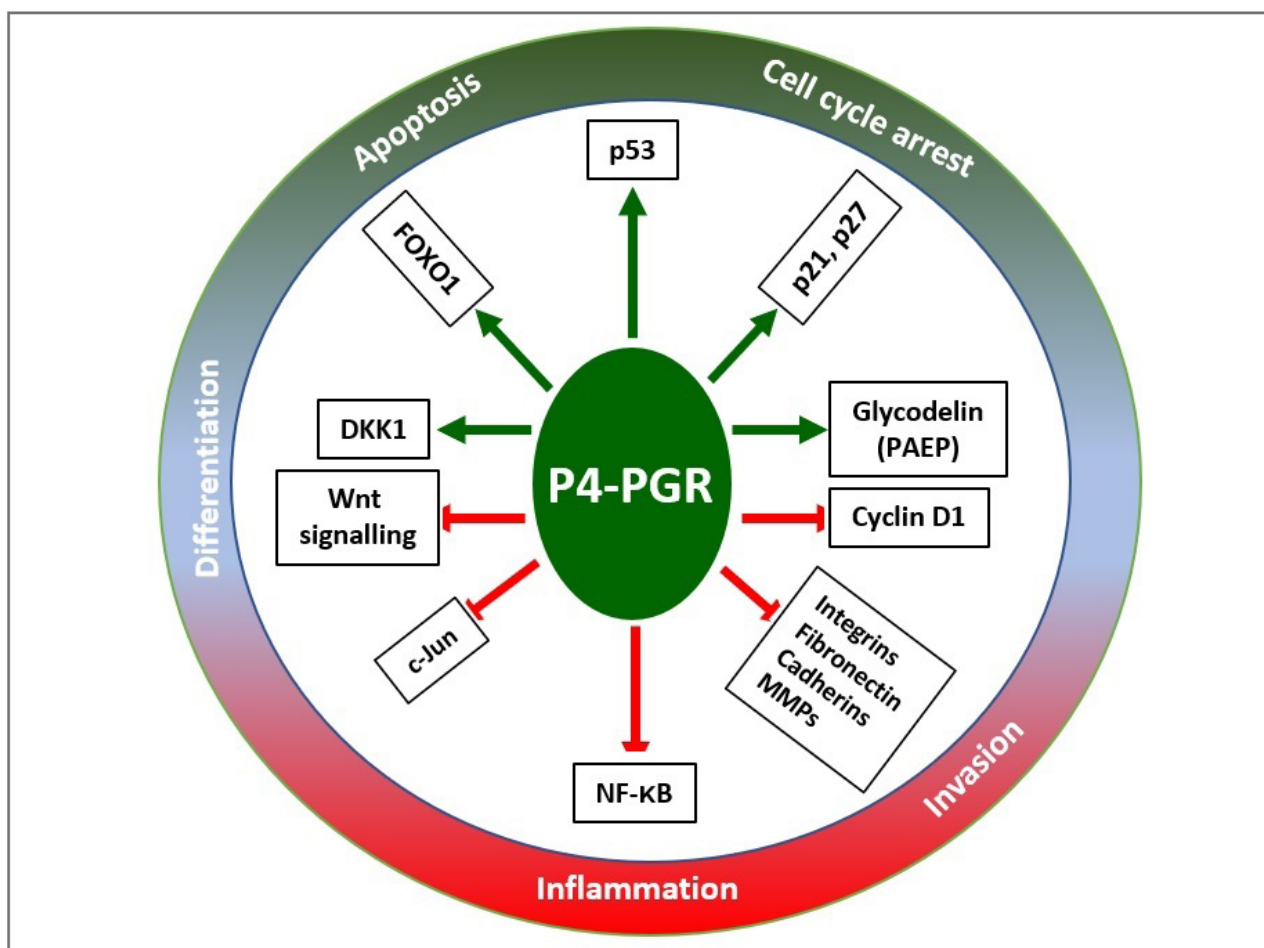
Ectopic Tissue

There is substantial evidence to suggest that progesterone resistance is a general feature of endometriotic lesion. [Table 1](#) lists some of the supporting studies. As mentioned above, progesterone treatment could not induce the conversion of oestradiol to oestrone in ectopic tissue.³² The enzyme 17 β -HSD2, which is responsible for catalysing the reaction, is upregulated by progesterone in secretory

epithelial cells of normal endometrium, but not by ectopic cells, providing the first-line evidence of progesterone resistance in endometriosis.⁵ In fact, PGR concentrations, for both PGR-A and PGR-B, in endometriosis tissue are generally repressed.^{6,33,34,44} Thus, it appears that attenuated PGR may result in altered gene transcription in ectopic tissue, even when progesterone concentration in circulation is normal.

Several large-scale gene expression studies revealed significant differences between ectopic and matching eutopic tissue. Many of the genes with differential expression were indeed progesterone target genes.^{37,38,42,43,45} In this regard, it is notable that there are reports of increased PGR expression in endometrioma, with a higher or unchanged PGR-B expression in endometrioma compared with normal endometrium.^{36,41} Interestingly, PGR expression was reportedly lower than in endometrium in primary endometriotic lesions, while in recurrent lesions there was no difference in PGR expression as compared with eutopic endometrium.⁴⁶ In another study, lower PGR expression was observed in stromal cells of ectopic lesions compared with eutopic tissue, while epithelial cells of ectopic lesion showed higher PGR expression in late secretory phase.³⁵

Figure 5: Progesterone mediated networks of regulatory pathways that promote (shown as the green arrow) cell cycle arrest, apoptosis, and differentiation, and inhibit (shown as the red blocked arrow) inflammation and invasion.



Adapted from Yang S et al.⁶⁷

DKK1: Dickkopf-related protein 1; FOXO1: Forkhead box protein O1; MMP: matrix metalloproteinase; NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; PAEP: human placental protein-14; PGR: progesterone receptor.

Eutopic Tissue

It is evident from the above discussion that ectopic tissue of females with endometriosis display suppressed PGR expression. The question whether a similar PGR suppression exists in the eutopic endometrium of females with endometriosis is rather unsettled. Table 2 provides a list of studies and the summary of results therein reflecting inconsistencies in this regard.

In a large-scale gene expression study, a higher clustering between proliferative and secretory

phase samples from eutopic endometrial biopsies as compared with normal endometrium was observed, and it was associated with a substantial number of PGR target genes being affected.⁴⁸ Collectively, these results were suggestive of inadequate progesterone-mediated transition of late proliferative to the early secretory phase in females with endometriosis.

Furthermore, there are studies indicating a decrease in the PGR-B:PGR-A ratio along with relatively high PGR-A expression in eutopic endometrium compared with normal

Table 1: A chronicle of reports regarding progesterone resistance in endometriotic lesion.

Name with year	Major relevant observation
Vierikko et al. ³²	Lack of induction of 17 β -HSD activity by progesterone, medroxy-progesterone acetate, or danazol was observed in endometriosis tissue along with lower concentration of PGR.
Prentice et al. ³³	Quantitatively lower immunopositive PGR expression was observed in endometriotic tissue compared to paired eutopic endometrium.
Bergqvist et al. ³⁴	Significantly lower expression of immunopositive PGR was observed in epithelial cells of ovarian endometriosis than in endometrial epithelial cells, but not in stromal cells.
Jones et al. ³⁵	Lower PGR expression in stromal cells of ectopic lesions compared with eutopic tissue, while epithelial cells of ectopic lesion showed higher PGR expression only in the late secretory phase.
Zeitoun et al. ⁵	Deficient 17 β -HSD2 expression, which is regulated by progesterone, was observed in endometriosis.
Misao et al. ³⁶	Dominant expression of PGR-B mRNA in ovarian endometriosis.
Attia et al. ⁶	PGR-A but not PGR-B was expressed in endometriosis.
Matsuzaki et al. ^{37,38}	Significantly higher levels of PGR regulated 17 β -HSD2 mRNA in epithelia of ectopic lesions of ovarian endometriosis compared with matched eutopic endometrium in secretory phase of menstrual cycle of ovarian endometriosis. No such difference was observed in deep endometriosis. In fact, 17 β -HSD2 expression was not detected in either epithelial or stromal cells of 50% ectopic samples.
Wu et al. ³⁹	Large-scale transcriptional characterisation of differences between eutopic and ectopic endometrium revealed 904 differentially expressed genes contributing to 79 pathways, with over 100 genes with known functions, including PGR dependent signalling systems (Wnt and MAPK signalling).
Bukulmez et al. ⁴⁰	Increased expression of PGR-C mRNA relative to PGR-A and PGR-B mRNA was observed in ovarian endometriosis compared with eutopic and control endometrium. The PGR-A protein was barely detectable in endometriomas. The significance of the observations lies in the fact that PGR-A and PGR-B serve an anti-inflammatory role in the uterus by antagonising NF- κ B activation and COX-2 expression, while PGR-C expression, which antagonises PGR-B, is associated with inflammation.
Smuc et al. ⁴¹	Expression analysis revealed no significant difference in expression of PGR-A and PGR-B in ovarian endometriosis compared with control endometrium despite indication of selective progesterone resistance (AKR1C1 and AKR1C3).
Khan et al. ^{42,43}	Genomic expressional profile of ectopic tissue differs from that of eutopic, suggestive of differential regulation in genes involved in physiological functions including progesterone action in inflammation, cell cycle, and death, along with relative downregulation of PGR in the secretory phase of ectopic endometrium, which is suggestive of relative suppression of progesterone action in ectopic lesion.
Bedaiwy et al. ⁴⁴	Abundance and localisation of progesterone receptor isoforms in endometrium in females with and without endometriosis and in peritoneal and ovarian endometriotic implants revealed PGR-A as the predominant isoform in peritoneal endometriosis, while both PGR-A and PGR-B were detected in ovarian endometriosis. However, PGR-A levels were significantly elevated in ovarian endometriosis compared with peritoneal endometriosis.

17 β -HSD: 17- β -hydroxysteroid dehydrogenase; 17 β -HSD2: 17- β -hydroxysteroid dehydrogenase Type 2; AKR1C1: aldo-keto reductase family 1 member C1; AKR1C3: aldo-keto reductase family 1 member C3; COX-2: cyclo-oxygenase-2; MAPK: mitogen-activated protein kinase; mRNA: messenger RNA; NF- κ B: nuclear factor κ -light-chain-enhancer of activated B cells; PGR: progesterone receptor.

Table 2: Summary of selected reports regarding progesterone resistance in eutopic endometrium during endometriosis.

Name with year	Major relevant observation
Jones et al. ³⁵	No marked difference in PGR expressions between normal endometrium and eutopic endometrium during endometriosis.
Attia et al. ⁶	PGR-A and PGR-B detected in eutopic endometrial samples, with increased levels in the pre-ovulatory phase with near normal cyclical variation.
Igarashi et al. ⁴⁷	Eutopic endometriotic endometrium of proliferative phase showed significantly lower PGR-B:PGR-A ratio than that in normal endometrium.
Matsuzaki et al. ³⁸	In eutopic endometrium from patients with deep endometriosis, 17 β -HSD2 expression in epithelial cells was significantly increased during the early, middle, and late secretory phases compared with the late proliferative phase. No such difference was detected in control endometrium.
Burney et al. ⁴⁸	Transcriptome analysis revealed reduced progesterone response in the transition from the proliferative to secretory phases in eutopic endometrium of females with endometriosis compared with normal endometrium.
Aghajanova et al. ^{49,50}	Isolated hESF from mid-secretory endometrium with and without endometriosis passaged <i>in vitro</i> and exposed to 8-Br-cAMP or progesterone displayed lower expression of decidualisation markers (IGFBP1 and prolactin) by hESF cells from females with endometriosis versus those without endometriosis in response to 8-Br-cAMP but not to progesterone. Decreased 3 β -HSD1 and 17 β -HSD2, and increased 17 β -HSD1 with a shift towards an estrogenic milieu in hESF cells of eutopic endometrium of endometriosis. The normal response of hESF to progesterone, which involves a tightly regulated kinetic cascade of PGR and MAPK signalling pathways, resulting in decidualisation was not established by progesterone in hESF cells of endometriosis.
Gentilini et al. ⁵¹	Both PGR-A and PGR-B expressed in endometrial stromal cells derived from females with and without endometriosis and grown as monolayers on plastic in 10% FBS containing medium was comparable.
Zelenko et al. ²³	The study revealed a blunted proliferative-to-secretory transition in early secretory phase endometrium of endometriosis, suggestive of progesterone resistance in endometrium of females with endometriosis.
Bedaiwy et al. ⁴⁴	In eutopic endometrium, levels of PGR-A were significantly elevated in females with endometriosis compared with females without disease, regardless of menstrual phase. Endometriotic lesions and eutopic endometrium from females with endometriosis are uniform in a PGR-A-dominant state.
Barragan et al. ³⁰	eSFs from endometriosis displayed a pro-inflammatory and progesterone resistance phenotype not detected in normal eSFs. The progesterone resistance in eSFs inherited from endometrial mesenchymal cells in endometriosis.
Anupa et al. ⁵²	Higher expression of 17 β -HSD1 and PGR-A in eutopic endometrium in endometriosis compared with normal endometrium, particularly during the secretory phase of the menstrual cycle. Dysregulated 17 β -HSD1 expression along with alterations in the PGR-A:PGR-B ratio, resulting in hyperoestrogenism and progesterone resistance during the secretory phase of the menstrual cycle, rather than an anomaly in aromatase expression as hallmarks of eutopic endometrium of patients with ovarian endometriosis who are infertile. Also, revealed that fertility and menstrual cycle histories exert differential effects on steroid physiology in endometrium from endometriosis patients compared with control subjects.

8-Br-cAMP; 8-bromoadenosine 3',5'-cyclic monophosphate; 17 β -HSD1: 17- β -hydroxysteroid dehydrogenase Type 1; 17 β -HSD2: 17- β -hydroxysteroid dehydrogenase Type 2; eSF: endometrial stromal fibroblasts; FB: fibroblast; hESF: human endometrial stromal fibroblasts; IGFBP1: insulin-like growth factor-binding protein 1; MAPK: mitogen-activated protein kinase; PGR: progesterone receptor.

endometrium.^{44,47,53} On the contrary, several studies failed to substantiate these findings. A cyclical variation in PGR expression in eutopic endometrium from females with endometriosis, which was comparable to normal cyclical endometrium was reported in an early report.³⁴ Further, several studies failed to mark any notable difference in the expression of PGR-A and PGR-B expression in normal and eutopic endometrium.^{6,35,51}

The reported inconsistencies in results of the previous studies on endometrial progesterone receptivity might have resulted from differences in the technical details (e.g., details of tissue collection and handling) and the lack of a categorical consideration of the relative effects of fertility and menstrual histories on PGR expression and actions in the endometrium of patients with and without endometriosis.⁵² Moreover, the reported studies on PGR response used isolated cells maintained in a 2D culture system, which might be an inadequate model for addressing the core issue of progesterone resistance due to the fact that such isolated cells often lose their differential behaviour typically seen in the tissue.^{31,49,50,54}

Additionally, the statistical design and clinical details in a few studies were not foolproof. The Endometriosis Phenome (and Biobanking) Harmonisation Project (EPHect) guidelines highlight the necessity of developing a consensus on the standardisation and harmonisation of phenotypic surgical and clinical data and biological sample handling methods in endometriosis research.^{55,56} In a recent controlled study conducted according to EPHect guidelines, lower levels of expression of aromatase and oestrogen receptor β along with higher 17 β -HSD1 and PGR-A in endometrium of females with ovarian endometriosis was observed.⁵² Thus, dysregulated expression of 17 β -HSD1 and PGR results in hyperoestrogenism and progesterone resistance during the secretory phase of the menstrual cycle, rather than an anomaly in aromatase expression, was the hallmark of eutopic endometrium from patients with ovarian endometriosis.⁵² It is now evident that fertility and menstrual cycle histories exert differentiating effects on endometrial physiology in females with endometriosis, vis-à-vis normal healthy endometrium.^{42,43,52}

MECHANISMS OF PROGESTERONE RESISTANCE IN ENDOMETRIOSIS

Collectively, it appears from different lines of evidence available that progesterone resistance in endometriosis is not an 'all-or-none' phenomenon, and that ectopic tissue exhibits higher order of progesterone resistance than eutopic tissue in a relative scale. Suppression of PGR expression and activity in target cells may potentially take place due to interference in transcriptional, post-transcriptional, and post-translational events, and at the level of protein stability. These events can reportedly be affected in endometriosis;^{23,57-61} however, progesterone receptor polymorphisms are not related to susceptibility to endometriosis.⁶² Fundamentally, it depends on genetic background, natural history of development of the individual, and the organ and macro- to micro-environmental details.

In an interesting study, Jackson et al.⁶³ demonstrated that PGR-A and PGR-B expression in the eutopic endometrium markedly reduced over time, between 3 and 15 months, after induction by using a model of experimental induction of endometriosis and implanting endometrial tissue into the peritoneal environment of a baboon.⁶³ In connection to this, McKinnon et al.¹⁰ presented an elegant model explaining how constant exposure to the inflammatory ecology in peritoneal environment may result in suppression of PGR expression and activity. It now appears that human endometrial fibroblasts display PGR resistance and an inflammatory phenotype, possibly due to epigenomic modifications in the endometrium during endometriosis.^{10,23,30,31,40,61} Although PGR gene expressions and PGR actions are significantly dysregulated in both eutopic and ectopic tissues compared with control endometrium, the underlying epigenetic mechanisms for PGR suppression in the eutopic tissue are different from ectopic tissue.^{57,64}

IMPLICATIONS OF PROGESTERONE RESISTANCE IN ENDOMETRIOSIS

Progesterone resistance in endometriosis has been implicated in four clinically challenging trade-offs: pain, infertility, inflammatory disorders, and neoplasm; these impair the quality of life of the patients.⁶⁵ Nearly 10% of females

of reproductive age have endometriosis, with more than 70% of them affected by chronic pelvic pain.⁶⁵ Endometriosis is also a well-acknowledged cause of infertility, which is seen in 50% of patients with endometriosis with normal ovulation and normo-spermic partners. Severe endometriosis is associated with poor embryo implantation rates and pregnancy rates in women undergoing *in vitro* fertilisation treatment.⁶⁵ Females with endometriosis often have several inflammation-linked and other comorbidities like uterine fibroid, adenomyosis, pelvic inflammatory disorder, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, fibromyalgia and cardiovascular diseases.⁶⁵ Endometriosis is generally considered benign; however, unmanaged endometriosis with atypia may result in ovarian and extra-ovarian cancers.⁶⁶

Based on generally known progesterone actions in target tissues as discussed above and shown in Figure 5, it appears that resistance of progesterone action may cause the above-mentioned endometriosis-associated conditions in patients.^{21,67} Yet, progestin treatment is met with failure in a large number of patients.^{7,8} Is it possible to overcome this resistance with the help of combinatorial therapies? For example, can the addition of a DNA methyltransferase inhibitor to reverse epigenetically suppressed PGR expression be helpful? The epigenetic modifications of PGR and progesterone target genes in eutopic and ectopic tissues may, however, be markedly different.^{57,64}

In primary endometriotic lesions, PGR expression is lower than in endometrium, generally having better prognosis with progesterone treatment. Meanwhile, there was no difference in PGR expression as compared with eutopic endometrium in recurrent lesions, generally having poor prognosis with progesterone treatment.⁴⁶

It is evident from the above-discussion that PGR (both PGR-A and PGR-B) expression status is not sufficient to understand the nature of progesterone resistance. Can there be a set of novel and more useful functional parameters? How is PGR expression and response in target cells from females with endometriosis affected by other linked molecular mechanisms?^{21,21,26,68,69} Several such unmet questions point to the fact that there is an urgent need for a better understanding of the nuanced characteristics of progesterone resistance in ectopic and eutopic tissue in endometriosis, to innovate better management and treatment of progesterone resistance in the future.

CONCLUSION

It has been more than half a century since the administration of progestins has become a part of the normalised procedure to treat endometriosis. Nevertheless, its success rate is limited as it fails with time and some patients do not respond to this therapy as expected. As the authors have discussed, such progesterone resistance occurs due to suppressed PGR expression, dysregulated downstream PGR actions, or both. In any case, estimated upscaling of dosage schedule or by small modifications in the molecular design of the drug cannot help in circumventing these issues. Success with available combinatorial approach is also not very promising. There is an urgent necessity for deeper and better understanding of the cellular and molecular issues related to progesterone resistance in endometriosis so that novel approaches may be innovated to restore the various homeostatic mechanisms disrupted by progesterone resistance in ectopic and eutopic tissues in endometriosis.

References

- Ghosh D, Sengupta J. Examining diagnostic options and classification systems available for endometriosis. *EMJ Repro Health.* 2021;7(1):60-71.
- Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol.* 1927;14:422-69.
- Redwine DB. Was Sampson wrong? *Fertil Steril.* 2002;78(4):686-93.
- Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril.* 1997;68(4):585-96.
- Zeitoun K et al. Deficient 17 β -hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17 β -estradiol. *J Clin Endocrinol Metab.* 1998;83(12):4474-80.
- Attia GR et al. Progesterone receptor isoform A but not B is expressed in endometriosis. *J Clin Endocrinol Metab.* 2000;85(8):2897-902.

7. Barra F et al. A comprehensive review of hormonal and biological therapies for endometriosis: latest developments. *Expert Opin Biol Ther.* 2019;19(4):343-60.
8. Reis FM et al. Progesterone receptor ligands for the treatment of endometriosis: the mechanisms behind therapeutic success and failure. *Hum Reprod Update.* 2020;26(4):565-85.
9. Patel BG et al. Progesterone resistance in endometriosis: origins, consequences and interventions. *Acta Obstet Gynecol Scand.* 2017;96(6):623-32.
10. McKinnon B et al. Progesterone resistance in endometriosis: an acquired property? *Trends Endocrinol Metab.* 2018;29(8):535-48.
11. Marquardt RM et al. Progesterone and estrogen signaling in the endometrium: What goes wrong in endometriosis? *Int J Mol Sci.* 2019;20(15):3822.
12. Donnez J, Dolmans MM. Endometriosis and medical therapy: from progestogens to progesterone resistance to GnRH antagonists: A review. *J Clin Med.* 2021;10(5):1085.
13. Graham JD, Clarke CL. Physiological action of progesterone in target tissues. *Endocr Rev.* 1997;18(4):502-19.
14. Scarpin KM et al. Progesterone action in human tissues: regulation by progesterone receptor (PR) isoform expression, nuclear positioning and coregulator expression. *Nucl Recept Signal.* 2009;7(12):e009.
15. Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand.* 2015;94(Suppl 161):8-16.
16. Medina-Laver Y et al. What do we know about classical and non-classical progesterone receptors in the human female reproductive tract? A Review. *Int J Mol Sci.* 2021;22(20):11278.
17. Patel B et al. Role of nuclear progesterone receptor isoforms in uterine pathophysiology. *Hum Reprod Update.* 2015;21(2):155-73.
18. Wu SP et al. Progesterone receptor regulation of uterine adaptation for pregnancy. *Trends Endocrinol Metab.* 2018; 29(7):481-91.
19. DeMayo FJ, Lydon JP. 90 years of progesterone: new insights into progesterone receptor signaling in the endometrium required for embryo implantation. *J Mol Endocrinol.* 2020;65(1):T1-14.
20. Jacobsen BM, Horwitz KB. Progesterone receptors, their isoforms and progesterone regulated transcription. *Mol Cell Endocrinol.* 2012;357(1-2):18-29.
21. Mani S, Portillo W. Activation of progesterone receptors in female reproductive behavior: Interactions with neurotransmitters. *Front Neuroendocrinol.* 2010;31(2):157-71.
22. Hill KK et al. Structural and functional analysis of domains of the progesterone receptor. *Mol Cell Endocrinol.* 2012;348(2):418-29.
23. Zelenko Z et al. Nuclear receptor, coregulator signaling, and chromatin remodeling pathways suggest involvement of the epigenome in the steroid hormone response of endometrium and abnormalities in endometriosis. *Reprod Sci.* 2012;19(2):152-62.
24. Garg D et al. Progesterone-mediated non-classical signaling. *Trends Endocrinol Metab.* 2017;28(9):656-68.
25. Conneely OM et al. Reproductive functions of progesterone receptors. *Recent Prog Horm Res.* 2002;57:339-55.
26. Lessey BA. Two pathways of progesterone action in the human endometrium: implications for implantation and contraception. *Steroids.* 2003;68(10-13):809-15.
27. Keller DW et al. Pseudocorpus luteum insufficiency: a local defect of progesterone action on endometrial stroma. *J Clin Endocrinol Metab.* 1979;48(1):127-32.
28. McKusick VA. Progesterone resistance. 2002. Available at: <https://omim.org/entry/264080>. Last accessed: 26 March 2022.
29. Chrousos GP et al., "Progesterone resistance," Chrousos GP et al. (eds), *Steroid Hormone Resistance: Mechanisms and Clinical Aspects* (1986) 7th edition, New York: Plenum Press, pp.317-32.
30. Barragan F et al. Human endometrial fibroblasts derived from mesenchymal progenitors inherit progesterone resistance and acquire an inflammatory phenotype in the endometrial niche in endometriosis. *Biol Reprod.* 2016;94(5):118.
31. Anupa G et al. Endometrial stromal cell inflammatory phenotype during severe ovarian endometriosis as a cause of endometriosis associated infertility. *Reprod Biomed Online.* 2020;41(4):623-39.
32. Vierikko P et al. Steroidal regulation of endometriosis tissue: lack of induction of 17 beta-hydroxysteroid dehydrogenase activity by progesterone, medroxyprogesterone acetate, or danazol. *Fertil Steril.* 1985;43(2):218-24.
33. Prentice A et al. Ovarian steroid receptor expression in endometriosis and in two potential parent epithelia: endometrium and peritoneal mesothelium. *Hum Reprod.* 1992;7(9):1318-25.
34. Bergqvist A et al. Immunohistochemical analysis of oestrogen and progesterone receptors in endometriotic tissue and endometrium. *Hum Reprod.* 1993;8(11):1915-22.
35. Jones RK et al. Immunohistochemical characterization of proliferation, oestrogen receptor and progesterone receptor expression in endometriosis: comparison of eutopic and ectopic endometrium with normal cycling endometrium. *Hum Reprod.* 1995;10(12):3272-9.
36. Misao R et al. Dominant expression of progesterone receptor form B mRNA in ovarian endometriosis. *Horm Res.* 1999;52(1):30-4.
37. Matsuzaki S et al. Analysis of aromatase and 17beta-hydroxysteroid dehydrogenase type 2 messenger ribonucleic acid expression in deep endometriosis and eutopic endometrium using laser capture microdissection. *Fertil Steril.* 2006(a);85(2):308-13.
38. Matsuzaki S et al. Differential expression of genes in eutopic and ectopic endometrium from patients with ovarian endometriosis. *Fertil Steril.* 2006(b);86(3):548-53.
39. Wu Y et al. Transcriptional characterizations of differences between eutopic and ectopic endometrium. *Endocrinology.* 2006;147(1):232-46.
40. Bukulmez O et al. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. *Endocrinology.* 2008;149(3):1190-204.
41. Smuc T et al. Disturbed estrogen and progesterone action in ovarian endometriosis. *Mol Cell Endocrinol.* 2009;301(1-2):59-64.
42. Khan MA et al. cDNA-based transcript analysis of autologous eutopic and ectopic endometrium of women with moderate and

- severe endometriosis. *Journal of Endometriosis*. 2011;3(1):8-33.
43. Khan MA et al. Genome-wide expressions in autologous eutopic and ectopic endometrium of fertile women with endometriosis. *Reprod Biol Endocrinol*. 2012;10(9):84.
 44. Bedaiwy MA et al. Abundance and localization of progesterone receptor isoforms in endometrium in women with and without endometriosis and in peritoneal and ovarian endometriotic implants. *Reprod Sci*. 2015;22(9):1153-61.
 45. Meola J et al. Differentially expressed genes in eutopic and ectopic endometrium of women with endometriosis. *Fertil Steril*. 2010;93(6):1750-73.
 46. Bergqvist A, Fernö M. Estrogen and progesterone receptors in endometriotic tissue and endometrium: comparison according to localization and recurrence. *Fertil Steril*. 1993; 60(1):63-8.
 47. Igarashi TM et al. Reduced expression of progesterone receptor-B in the endometrium of women with endometriosis and in cocultures of endometrial cells exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fertil Steril*. 2005;84(1):67-74.
 48. Burney RO et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology*. 2007;148(8):3814-26.
 49. Aghajanova L et al. Steroidogenic enzyme and key decidualization marker dysregulation in endometrial stromal cells from women with versus without endometriosis. *Biol Reprod*. 2008;80(1):105-14.
 50. Aghajanova L et al. Unique transcriptome, pathways, and networks in the human endometrial fibroblast response to progesterone in endometriosis. *Biol Reprod*. 2011; 84(4):801-15.
 51. Gentilini D et al. Endometrial stromal progesterone receptor-A/ progesterone receptor-B ratio: no difference between women with and without endometriosis. *Fertil Steril*. 2010;94(4):1538-40.
 52. Anupa G et al. An assessment of the multifactorial profile of steroid-metabolizing enzymes and steroid receptors in the eutopic endometrium during moderate to severe ovarian endometriosis. *Reprod Biol Endocrinol*. 2019;17(1):111.
 53. Petousis S et al. Unexplained infertility patients present the mostly impaired levels of progesterone receptors: prospective observational study. *Am J Reprod Immunol*. 2018;79(6):e12828.
 54. Cukierman E et al. Cell interactions with three-dimensional matrices. *Curr Opin Cell Biol*. 2002;14(5):633-9.
 55. Fassbender A et al.; WERF EPHeC Working Group. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: IV. Tissue collection, processing, and storage in endometriosis research. *Fertil Steril*. 2014;102(5):1244-53.
 56. Miller LM, Johnson NP. EPHeC - the Endometriosis Phenome (and Biobanking) Harmonisation Project - may be very helpful for clinicians and the women they are treating. *F1000Res*. 2017;6:14.
 57. Wu Y et al. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in endometriosis. *Epigenetics*. 2006;1(2):106-11.
 58. Teague EM et al. The role of microRNAs in endometriosis and associated reproductive conditions. *Hum Reprod Update*. 2010;16(2):142-65.
 59. Meyer JL et al. DNA methylation patterns of steroid receptor genes ESR1, ESR2 and PGR in deep endometriosis compromising the rectum. *Int J Mol Med*. 2014;33(4):897-904.
 60. Rocha-Junior CV et al. Progesterone receptor B (PGR-B) is partially methylated in eutopic endometrium from infertile women with endometriosis. *Reprod Sci*. 2019;26(12):1568-74.
 61. MacLean JA II, Hayashi K. Progesterone actions and resistance in gynecological disorders. *Cells*. 2022;11(4):647.
 62. Carneiro PP et al. Association of genetic polymorphisms of estrogen and progesterone receptors and endometriosis: Meta-analysis. *J Endometr Pelvic Pain Disord*. 2019;11(1):25-36.
 63. Jackson KS et al. The altered distribution of the steroid hormone receptors and the chaperone immunophilin FKBP52 in a baboon model of endometriosis is associated with progesterone resistance during the window of uterine receptivity. *Reprod Sci*. 2007;14(2):137-50.
 64. Esfandiari F et al. Disturbed progesterone signalling in an advanced preclinical model of endometriosis. *Reprod Biomed Online*. 2021;43(1):139-147.
 65. Ghosh D et al. Pathophysiological basis of endometriosis-linked stress associated with pain and infertility: a conceptual review. *Reprod Med*. 2020;1(1):32-61.
 66. Ghosh D et al. How benign is endometriosis: multi-scale interrogation of documented evidence. *Cur Op Gyn Obs*. 2019;2(1):318-45.
 67. Yang S et al. Progesterone: the ultimate endometrial tumor suppressor. *Trends Endocrinol Metab*. 2011;22(4):145-52.
 68. Li Y et al. Progesterone alleviates endometriosis via inhibition of uterine cell proliferation, inflammation and angiogenesis in an immunocompetent mouse model. *PLoS One*. 2016;11(10):e0165347.
 69. Lode L et al. Abnormal pathways in endometriosis in relation to progesterone resistance: a review. *J Endometr Pelvic Pain Disord*. 2017;9(4):245-51.

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