Published in final edited form as:

Semin Reprod Med. 2010 January ; 28(1): 44–50. doi:10.1055/s-0029-1242992.

17 β -Hydroxysteroid Dehydrogenase-2 Deficiency and Progesterone Resistance in Endometriosis

Serdar E. Bulun, M.D.¹, You-Hong Cheng, Ph.D.¹, Mary Ellen Pavone, M.D.¹, Ping Yin, Ph.D.¹, Gonca Imir, M.D.², Hiroki Utsunomiya, M.D.³, Stephen Thung, M.D.⁴, Qing Xue, M.D., Ph.D.⁵, Erica E. Marsh, M.D.¹, Hideki Tokunaga, M.D., Ph.D.³, Hiroshi Ishikawa, M.D., Ph.D.⁶, Takeshi Kurita, Ph.D.¹, and Emily J. Su, M.D., M.S.¹

¹Division of Reproductive Biology Research, Department Obstetrics and Gynecology Northwestern University Feinberg School of Medicine, Chicago, Illinois

²Department of Obstetrics and Gynecology, Cunkhuriyet University School of Medicine, Sivas, Turkey

³Department of Obstetrics and Gynecology, Tohoku University School of Medicine, Sendai, Japan

⁴Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut

⁵Department of Obstetrics and Gynecology, First Hospital of Peking University, Beijing, P.R. China

⁶Department of Reproductive Medicine, Chiba University, Inohana Chuo-ku, Chiba, Japan

Abstract

Estradiol (E2) stimulates the growth and inflammation in the ectopic endometriotic tissue that commonly resides on the pelvic organs. Several clinical and laboratory-based observations are indicative of resistance to progesterone action in endometriosis. The molecular basis of progesterone resistance in endometriosis may be related to an overall reduction in the levels of progesterone receptor (PR). In normal endometrium, progesterone acts via PR on stromal cells to induce secretion of paracrine factor(s) that in turn stimulate neighboring epithelial cells to express the enzyme 17 β -hydroxysteroid dehydrogenase type 2 (HSD17B2). HSD17B2 is an extremely efficient enzyme and rapidly metabolizes the biologically potent estrogen E2 to weakly estrogenic estrone. In endometriotic tissue, progesterone is incapable of inducing epithelial HSD17B2 expression due to a defect in stromal cells. The inability of endometriotic stromal cells to produce progesterone-induced paracrine factors that stimulate HSD17B2 may be due to the very low levels of PR observed in vivo in endometriotic tissue. The end result is deficient metabolism of E2 in endometriosis giving rise to high local concentrations of this mitogen. The molecular details of this physiological paracrine interaction between the stroma and epithelium in normal endometrium and its lack thereof in endometriosis are discussed.

Keywords

17 β -HSD-2; HSD17B2; endometriosis; endometrium; estradiol; progesterone; receptor; resistance; retinoic acid; paracrine; epithelial-stromal

The most important known functions of progesterone in women are the preparation of endometrium for implantation and maintenance of pregnancy. Progesterone action is also essential for secondary development of the mammary gland. The effects of progesterone are mediated via intracellular progesterone receptors (PRs) that are transcribed from a single gene as two isoforms. These isoforms are progesterone receptor A (PR-A) and progesterone receptor B (PR-B)¹ (Fig. 1). PR-A is a 94-kDa protein; PR-B is an ~114-kDa protein that contains an additional 164 amino acids at its amino terminal.²⁻⁴ PR-A and PR-B may arise as a result of either initiation of translation from alternative sites in the same mRNA⁵ or by transcription from alternative promoters in the same gene.¹ Although this has been debated, use of alternative promoters giving rise to distinct mRNA species specific for PR-A and PR-B seems to be the likely mechanism.⁶

The existence of multiple PR isoforms may partially explain the complex and diverse biological actions of the progestins. PR-B and the PR-A have different transcriptional functions that are cell and promoter specific. Generation of knockout mice with selective ablation of PR-A or PR-B has provided in vivo proof that each isoform mediates distinct actions of progesterone. PR-A is both necessary and sufficient to elicit the progesterone-dependent uterine and ovarian responses necessary for female fertility, whereas the PR-B isoform is required to elicit normal responses of the mammary gland to progesterone.⁷

In human endometrial tissue, PR-B is likely to play a more important biological role in the endometrium because PR-B, but not PR-A, levels are tightly regulated by estradiol (E2) during the human menstrual cycle.^{8,9} The in vivo distribution of PR-A and PR-B in the endometrium was reported to be cell and cycle specific, further supporting the hypothesis that PR-A and PR-B may have distinct physiological roles.¹⁰

PARACRINE GENE REGULATION BY PROGESTERONE RECEPTOR IN ENDOMETRIUM

Progesterone induces the differentiation of both endometrial stromal and epithelial cells as exemplified by decidual and secretory changes and reduction in epithelial cell proliferation. The histological markers of differentiation, stromal decidualization and epithelial secretion, are associated with the presence of nuclear PRs and increased levels of circulating progesterone during the luteal phase. Molecular markers of progesterone action with respect to differentiation include increased production of lactoferrin and glycodelin in epithelial cells and prolactin and insulinlike growth factor binding protein-1 (IGFBP-1) in stromal cells of the endometrium.

Progesterone inhibits and even reverses estrogen-induced endometrial growth, hyperplasia, or adenocarcinoma of the endometrium. This effect was found to be mediated by PR in stromal cells in tissue recombination studies of PR knockout and wild-type mice.¹¹ These

findings reinforced the concept that progesterone-dependent stromal cell-derived factors act on epithelial cells to offset the effects of estrogen.

The antiestrogenic effect of progesterone in endometrial tissue is in part mediated by its stimulation of 17 β -hydroxysteroid dehydrogenase type 2 activity, which catalyzes the conversion of biologically active E2 to the inactive steroid estrone (E1).^{12–14} 17 β -hydroxysteroid dehydrogenase type 2 catalyzes the conversions of E2→E1 and testosterone→androstenedione in the endometrium as well as in the placenta and liver.¹⁵ This enzyme is encoded by the *HSD17B2* gene in endometrial epithelial cells^{16,17} (Fig. 2). Very high levels of HSD17B2 mRNA have been demonstrated in the epithelial cell component of whole endometrial tissue upon exposure to progesterone both in vivo and in vitro.^{16,17}

Direct treatment of isolated endometrial epithelial cells with progesterone only slightly induced HSD17B2 expression. We found, however, that endometrial epithelial HSD17B2 expression was regulated robustly by soluble factors in conditioned medium from endometrial stromal cells incubated with progesterone.¹⁸ Stromal PRs mediated progesterone-dependent production of a cocktail that stimulated epithelial HSD17B2 promoter activity, mRNA, and enzyme activity¹⁸ (Fig. 2). Serial deletion analysis of the HSD17B2 promoter showed that the 200 bp region immediately upstream of the transcription start site was essential for the maximum stromal PR-dependent induction of this epithelial promoter.¹⁸ Site-directed mutants of the HSD17B2 promoter demonstrated that two overlapping specificity protein 1 (Sp1) motifs within this critical regulatory region are essential for induction of promoter activity by stromal cell-conditioned medium or overexpression of Sp1/Sp3.¹⁹ Conditioned medium markedly enhanced binding of Sp1/Sp3 to this region of the HSD17B2 promoter. In vivo, we demonstrated a significant spatiotemporal association between epithelial Sp1/Sp3 and HSD17B2 protein levels in human endometrial biopsies.¹⁹ Taken together, these data suggest that HSD17B2 expression in endometrial epithelial cells, and therefore E2 inactivation, is regulated by Sp1 and Sp3, which are downstream targets of progesterone-dependent paracrine signals originating from endometrial stromal cells (Fig. 2).¹⁹

We also found that 9-cis or all-trans retinoic acid (RA) stimulated HSD17B2 expression in endometrial epithelial cells.²⁰ The liganded RA receptors RAR α /RXR α tethered Sp1/Sp3 at the HSD17B2 promoter to induce its activity²⁰ (Fig. 2). The Sp1-binding cis-regulatory site at HSD17B2 promoter, Sp1, Sp3, RAR α , and RXR α were all necessary for RA-dependent stimulation of HSD17B2 expression in endometrial epithelial cells.²⁰ Taken together, these findings suggest that progesterone acts on endometrial stromal cell PR to stimulate formation of paracrine factors including RA. This in turn activates RA- and Sp1/Sp3-dependent signaling to up-regulate HSD17B2 expression in endometrial epithelial cells leading to conversion of E2 to E1.²⁰

Impaired Differentiation of Endometriotic Stromal Cells in Response to a Progestin²¹

We characterized primary endometriotic stromal cells by demonstrating prolactin mRNA expression in response to treatment with medroxyprogesterone acetate (MPA) and dibutyryl cyclic adenosine monophosphate (Bt₂cAMP).²¹ Prolactin is a molecular marker of

decidualization of endometrial stromal cells. Prolactin mRNA was detected in cultured stromal cells from eutopic endometrium and endometriosis but not in ovarian granulosa and theca cells.²¹ Progesterone-induced prolactin mRNA levels in endometriotic cells were much lower compared with eutopic endometrial cells.²¹ These findings further support the concept of impaired stromal differentiation owing to a relative resistance to progesterone action in endometriosis.

Progesterone Receptor-B and Total Progesterone Receptors Are Significantly Decreased in Endometriotic Tissues and Cells⁹

Previous immunohistochemical studies revealed that PR levels are lower in endometriotic tissue compared with eutopic endometrium.^{22–24} The molecular evidence of progesterone resistance in endometrial tissues and cells, together with the clinical observation of resistance of endometriosis to treatment with progestins, prompted us to determine the protein and mRNA levels of PR-B and total PR in matched eutopic endometrial and endometriotic tissues exposed to the same circulating hormones.

In eutopic endometrium, PR-B protein and mRNA levels progressively increased during the proliferative phase, peaked immediately before ovulation, and diminished after ovulation, suggesting that E2 stimulates PR-B levels.⁹ In contrast, PR-B mRNA and protein levels were not detectable in any of the matched extraovarian eutopic endometrial samples (Fig. 1). In a separate matched tissue set of eutopic endometrial samples and ovarian endometrioma cyst walls, Affymetrix gene microarray (confirmed by real-time polymerase chain reaction [PCR]) showed severely decreased PR-B (11-fold) and total PR (8-fold) mRNA levels. These data suggest that the absence of PR-B protein in endometriotic tissue is transcription related (our unpublished observations). These *in vivo* observations in PR expression were accompanied by comparable differences in primary endometrial and endometriotic stromal cells in that both PR-B and PR-A levels are significantly lower in endometriotic stromal cells (our unpublished observations). Thus progesterone resistance in endometriotic tissue may be due to an overall reduction in PR and the absence of PR-B.⁹

Deficient Expression of HSD17B2 in Endometriosis²⁵

It was previously reported that progesterone did not induce the conversion of E2→E1 in endometriotic tissue, in contrast to eutopic endometrium.²⁶ Interconversions of E2 ↔ E1 are catalyzed by several enzymes encoded by separate genes.^{15,27,28} For example, HSD17B1 favors the formation of E2, whereas HSD17B2 encodes the most efficient enzyme for inactivation of E2 by conversion to E1.^{12,13,16} HSD17B2 enzyme activity and mRNA were found to be present in extremely high levels in eutopic endometrial tissues and epithelial cells (from disease-free women) during the secretory phase.^{12,13,16}

We demonstrated that HSD17B2 mRNA and protein are readily detectable in secretory eutopic endometrium but not in paired extraovarian endometriotic samples exposed to the same circulating levels of progesterone.²⁵ Immunoreactive HSD17B2 was localized to secretory epithelial cells. The lack of HSD17B2 in endometriotic epithelial cells of matched tissues despite histologically detectable secretory changes in response to progesterone suggested that endometriotic tissue exhibits selective resistance to certain actions of

progesterone. We also observed that inactivation of E2 is impaired in endometriotic tissues due to deficient expression of HSD17B2, which is normally expressed in eutopic endometrium in response to progesterone.²⁵

Furthermore, aberrant aromatase expression in endometriotic stromal cells favors the conversion of androstenedione to E1; aromatase expression is normally absent in the eutopic endometrium.²⁹ We also demonstrated that transcripts of the reductive HSD17B1, which catalyzes the conversion of E₁→E₂, were present in both eutopic endometrium and endometriotic tissue.²⁵ Thus the weakly estrogenic product of the aromatase reaction, E1, is readily converted to the potent estrogen, E2, in endometriotic tissues. Local concentrations of E2 in endometriotic tissues are further amplified by the lack of HSD17B2 expression and subsequent metabolism of E₂→E₁. Taken together, multiple molecular mechanisms contribute to the increased estrogenic activity in endometriosis as compared with eutopic endometrial tissue.

A Stromal Cell Defect Is Responsible for Deficient HSD17B2 Expression in Endometriotic Tissue

Physiologically, a stromal PR-mediated paracrine mechanism is responsible for induction of epithelial HSD17B2 expression. Paracrine factors secreted from stromal cells induce epithelial cells to produce the transcription factor Sp1 that binds to the promoter of the 17βHSD2 gene to regulate its expression.¹⁹ In contrast to eutopic endometrium, epithelial cells of endometriosis do not express HSD17B2 in vivo in response to progesterone, resulting in accumulation of E2 in ectopic tissue.²⁵

We attempted to determine the underlying cellular mechanism for this lack of HSD17B2 expression in endometriotic epithelial cells. The addition of conditioned medium from progestin-pretreated endometrial stromal cells significantly stimulated Sp1 protein and HSD17B2 mRNA and promoter activity in endometrial epithelial cells.³⁰ In contrast, conditioned medium from endometriotic stromal cells failed to induce Sp1 or HSD17B2 in epithelial cells (Fig. 3). Moreover, conditioned medium from progestin-pretreated endometrial stromal but not from endometriotic stromal cells enhanced binding of Sp1 to the HSD17B2 promoter region.³⁰ Taken together, a stromal cell defect in endometriosis appears to be responsible for the lack of progesterone-mediated secretion of factors that induce Sp1 production and its binding activity to the HSD17B2 promoter for expression of this gene in epithelial cells.³⁰ This may be a key molecular consequence clinically observed progesterone resistance in endometriosis (Fig. 3).

SUMMARY

Existing evidence points to a differentiation defect in endometriotic stromal cells due to resistance to selective actions of progesterone. Progesterone resistance in endometriosis seems to be subtle and manifested by specific molecular abnormalities. It is likely that progesterone resistance is primarily due to significantly lower PR-B and total PR in endometriotic stromal cells compared with endometrial stromal cells. PR deficiency is likely responsible for increased levels of E2 in endometriosis because progesterone fails to induce the E2-metabolizing enzyme HSD17B2 in endometriotic tissue (Fig. 3). We localized

deficient progesterone action to a stromal cell defect in endometriosis. Our conclusion resonates with gene expression microarray studies performed on eutopic endometrium of women with endometriosis compared with that from disease-free women.^{31,32} These studies on eutopic endometrium identified distinct molecular defects that are consistent with the progesterone resistance hypothesis.

Acknowledgments

This work was supported by grants from the NICHD (HD038691, to S.E.B.) and Friends of Prentice (to S.E.B.).

References

1. Kastner P, Krust A, Turcotte B, et al. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO J*. 1990; 9(5):1603–1614. [PubMed: 2328727]
2. Horwitz KB, Alexander PS. In situ photolinked nuclear progesterone receptors of human breast cancer cells: subunit molecular weights after transformation and translocation. *Endocrinology*. 1983; 113(6):2195–2201. [PubMed: 6685620]
3. Alexander IE, Clarke CL, Shine J, Sutherland RL. Progestin inhibition of progesterone receptor gene expression in human breast cancer cells. *Mol Endocrinol*. 1989; 3(9):1377–1386. [PubMed: 2608065]
4. Lessey BAAP, Alexander PS, Horwitz KB. The subunit structure of human breast cancer progesterone receptors: characterization by chromatography and photoaffinity labeling. *Endocrinology*. 1983; 112(4):1267–1274. [PubMed: 6682030]
5. Conneely OM, Sullivan WP, Toft DO, et al. Molecular cloning of the chicken progesterone receptor. *Science*. 1986; 233(4765):767–770. [PubMed: 2426779]
6. Giangrande PH, McDonnell DP. The A and B isoforms of the human progesterone receptor: two functionally different transcription factors encoded by a single gene. *Recent Prog Horm Res*. 1999; 54:291–313. discussion 313–314. [PubMed: 10548881]
7. Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. *Science*. 2000; 289(5485):1751–1754. [PubMed: 10976068]
8. Mangal RK, Wiehle RD III, Poindexter AN III, Weigel NL. Differential expression of uterine progesterone receptor forms A and B during the menstrual cycle. *J Steroid Biochem Mol Biol*. 1997; 63(4–6):195–202. [PubMed: 9459185]
9. Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR, Bulun SE. Progesterone receptor isoform A but not B is expressed in endometriosis. *J Clin Endocrinol Metab*. 2000; 85(8):2897–2902. [PubMed: 10946900]
10. Mote PA, Balleine RL, McGowan EM, Clarke CL. Colocalization of progesterone receptors A and B by dual immunofluorescent histochemistry in human endometrium during the menstrual cycle. *J Clin Endocrinol Metab*. 1999; 84(8):2963–2971. [PubMed: 10443705]
11. Kurita TLK, Lee KJ, Cooke PS, Lydon JP, Cunha GR. Paracrine regulation of epithelial progesterone receptor and lactoferrin by progesterone in the mouse uterus. *Biol Reprod*. 2000; 62(4):831–838. [PubMed: 10727250]
12. Tseng L, Gursipide E. Estradiol and 20 α -dihydroprogesterone dehydrogenase activities in human endometrium during the menstrual cycle. *Endocrinology*. 1974; 94(2):419–423. [PubMed: 4359125]
13. Tseng L, Gursipide E. Induction of human endometrial estradiol dehydrogenase by progestins. *Endocrinology*. 1975; 97(4):825–833. [PubMed: 172318]
14. Satyaswaroop PG, Wartell DJ, Mortel R. Distribution of progesterone receptor, estradiol dehydrogenase, and 20 α -dihydroprogesterone dehydrogenase activities in human endometrial glands and stroma: progestin induction of steroid dehydrogenase activities in vitro is restricted to the glandular epithelium. *Endocrinology*. 1982; 111(3):743–749. [PubMed: 6955172]

15. Wu LEM, Einstein M, Geissler WM, Chan HK, Elliston KO, Andersson S. Expression cloning and characterization of human 17 beta-hydroxysteroid dehydrogenase type 2, a microsomal enzyme possessing 20 alpha-hydroxysteroid dehydrogenase activity. *J Biol Chem.* 1993; 268(17):12964–12969. [PubMed: 8099587]
16. Casey ML, MacDonald PC, Andersson S. 17b-Hydroxysteroid dehydrogenase type 2: chromosomal assignment and progestin regulation of gene expression in human endometrium. *J Clin Invest.* 1994; 94:2135–2141. [PubMed: 7962560]
17. Mustonen MV, Isomaa VV, Vaskivuo T, et al. Human 17b-hydroxysteroid dehydrogenase type 2 messenger ribonucleic acid expression and localization in term placenta and in endometrium during the menstrual cycle. *J Clin Endocrinol Metab.* 1998; 83:1319–1324. [PubMed: 9543162]
18. Yang S, Fang Z, Gurates B, et al. Stromal progesterone receptors mediate induction of 17beta-hydroxysteroid dehydrogenase type 2 expression in human endometrial epithelium: a paracrine mechanism for inactivation of estradiol. *Mol Endocrinol.* 2001; 15:2093–2105. [PubMed: 11731611]
19. Cheng YH, Imir A, Suzuki T, et al. SP1 and SP3 mediate progesterone-dependent induction of the 17beta hydroxysteroid dehydrogenase type 2 gene in human endometrium. *Biol Reprod.* 2006; 75(4):605–614. [PubMed: 16807381]
20. Cheng YH, Yin P, Xue Q, Yilmaz B, Dawson MI, Bulun SE. Retinoic acid (RA) regulates 17beta-hydroxysteroid dehydrogenase type 2 expression in endometrium: interaction of RA receptors with specificity protein (SP) 1/SP3 for estradiol metabolism. *J Clin Endocrinol Metab.* 2008; 93(5):1915–1923. [PubMed: 18270252]
21. Bulun SE, Cheng YH, Yin P, et al. Progesterone resistance in endometriosis: link to failure to metabolize estradiol. *Mol Cell Endocrinol.* 2006; 248(1–2):94–103. [PubMed: 16406281]
22. Prentice A, Randall BJ, Weddell A, et al. Ovarian steroid receptor expression in endometriosis and in two potential parent epithelia: endometrium and peritoneal mesothelium. *Hum Reprod.* 1992; 7:1318–1325. [PubMed: 1479018]
23. Bergqvist A, Ferno M. Oestrogen and progesterone receptors in endometriotic tissue and endometrium: comparison of different cycle phases and ages. *Hum Reprod.* 1993; 8(12):2211–2217. [PubMed: 8150926]
24. Bergqvist A, Fernö M. Estrogen and progesterone receptors in endometriotic tissue and endometrium: comparison according to localization and recurrence. *Fertil Steril.* 1993; 60(1):63–68. [PubMed: 8513960]
25. Zeitoun KM, Takayama K, Sasano H, et al. Deficient 17beta-hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17beta-estradiol. *J Clin Endocrinol Metab.* 1998; 83(12):4474–4480. [PubMed: 9851796]
26. Vierikko PKA, Kauppila A, Rönnberg L, Vihko R. 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):218–224. [PubMed: 2981748]
27. Isomaa VV, Ghersevich SA, Mäentausta OK, Peltoketo EH, Poutanen MH, Vihko RK. Steroid biosynthetic enzymes: 17 beta-hydroxysteroid dehydrogenase. *Ann Med.* 1993; 25(1):91–97. [PubMed: 8382071]
28. Labrie F, Luu-The V, Labrie C, et al. Characterization of two mRNA species encoding human estradiol 17beta-dehydrogenase and assignment of the gene to chromosome 17. *J Steroid Biochem.* 1989; 34:189–197. [PubMed: 2483219]
29. Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. *Fertil Steril.* 1997; 68(3):393–401. [PubMed: 9314903]
30. Cheng YH, Imir A, Fenkci V, Yilmaz MB, Bulun SE. Stromal cells of endometriosis fail to produce paracrine factors that induce epithelial 17beta-hydroxysteroid dehydrogenase type 2 gene and its transcriptional regulator Sp1: a mechanism for defective estradiol metabolism. *Am J Obstet Gynecol.* 2007; 196:391–398. [PubMed: 17403431]
31. Kao LC, Germeyer A, Tulac S, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology.* 2003; 144(7):2870–2881. [PubMed: 12810542]

32. Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology*. 2007; 148(8):3814–3826. [PubMed: 17510236]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Progesterone receptor (PR)-B and PR-A protein detected by immunoprecipitation-western blot using samples of endometrium of patients with endometriosis (upper panel) and simultaneously biopsied matched samples of extraovarian endometriotic tissue (lower panel). Lanes 1 to 9 contain samples from nine women on cycle days indicated below each lane. Lane 10: No antibody was used during the immunoprecipitation procedure of endometrium (-ab, negative control for the top blot), and disease-free peritoneum was included as a negative control for the bottom blot (-per). Protein extract from T47D breast cancer cell line in lane 11 was used as a positive control.

Figure 2.

In endometrium, progesterone via stromal progesterone receptors (PR) stimulates formation of retinoic acid (RA) and other paracrine factors, which act on neighboring epithelial cells. These paracrine factors stimulate specificity protein (Sp)1 and Sp3 expression and recruitment of an enhancer transcriptional complex, composed of Sp1, Sp3, and retinoic acid (RA) receptors RAR α and RXR α , to the promoter of the 17 β -hydroxysteroid dehydrogenase-2 (HSD17B2) gene. This leads to the expression of the enzyme HSD17 β 2 that inactivates estradiol via conversion to estrone.

Figure 3.

Stromal cells of endometriosis are not capable of responding to progesterone by formation of sufficient quantities of retinoic acid (RA) and other paracrine factors because of deficient levels of progesterone receptor (PR). Consequently, 17 β -hydroxysteroid dehydrogenase-2 (HSD17B2) promoter in epithelial cells is not activated. HSD17B2 enzyme deficiency leads to high levels of tissue estradiol due to its decreased conversion to estrone.