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Progestins/Antiprogestins: Role in Pathogenesis and Treatment for Endometriosis

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Abstract

Endometriosis is a painful gynecological condition in fertile age in which endometrial tissue, which is normally found only in the inside lining of the uterus, develops outside the uterus and attaches to the pelvic floor, endometrium or peritoneal cavity. Endometriosis causes abdominal pain, bleeding, irregular menstrual cycles with excessive pain, inflammatory responses and infertility. Retrogressive menstruation and invasion theories have been well studied in the pathogenesis of endometriosis. The role of steroids including estrogen and gonadotropin releasing hormones has been documented and major treatment strategies are based on steroid biology of endometriosis. Current treatment strategies are only partly successful and focus solely on the late phase of the disease. The exact role of progesterone in the initiation (initial phase) of endometriosis has not been well studied or has been overshadowed by the concept of progesterone resistance that occurs in the late phase of endometriosis. In this review, we discuss the role of progesterone and the potential use of antiprogestins or possible combination treatment strategies that may help to combat initiation and progression of endometriosis.

Keywords: Endometriosis; Progesterone; Antiprogestins; Focal Adhesion Kinase (FAK); Personalized therapy

Endometriosis is a benign gynecological disease that affects about 10% of reproductive- age women. It is associated with pelvic pain and is a significant cause of infertility [1]. Patients with endometriosis show reduced rates of follicular growth, reduced functional ability of the pre-ovulatory follicle, reduced fertilization rates, irregular pre-implantation embryonic development, altered early luteal function, and reduced implantation rates [2,3]. Classical treatments, including progestins, antiestrogens and GnRH antagonists, often lead to undesirable side effects and a compromised quality of life [4]. Endometriosis is expensive to treat and complex to study because there are notable delays in its diagnosis as well as variations in symptoms and disease development in patients [5]. Also, at the time of clinical presentation, most women already have established disease, making the initiation ofendometriosis difficult to study. The implantation hypothesis of retrograde menstruation by Sampson [6] is the most widely accepted theory of endometriosis. Although retrograde menstruation occurs in all women, the reason thatonly 10% of women experience adhesion and invasion of endometriotic epithelial and stromal cells on peritoneal mesothelium remains elusive.

Only sparse reports are available regarding the molecular signalling of endometrial pathogenesis leading to the initiation and progression of endometriosis. A large body of scientific evidence suggests that estrogen and estrogen receptors (ERs) are involved in the progression of endometriosis [7]. Although progestins are used to treat endometriosis, the exact role of progesterone in the formation (initiation) of endometriotic lesions is poorly understood. The main side effects of progestin therapies are interim bleeding, weight gain and reduced libido. Oral contraceptives are generally well tolerated but they are not as effective in reducing pain [8]. GnRH-antagonists are highly effective, but they lead to a significant reduction in bone density [9]. Progesterone is produced by the corpus luteum to maintain early pregnancy. Low progesterone secretion in the luteal phase has been associated with habitual abortion. Hence it is logical to hypothesize that antiprogestins given in early pregnancy can act as abortifaciants and could provide alternatives to surgical abortion.

Based on our laboratory experiments, progression of endometriosis primarily depends on the levels of progesterone secretion by the corpus luteum at the time of attachment of menstrual endometrial epithelial/stromal cells to peritoneal mesothelium. Progesterone level is maintained high enough to support the attachment and subsequent invasion; then it drops dramatically after 1-2 weeks. This window is crucial for progesterone-induced proliferation and activation of progesterone target genes to ease the cellular invasion of the attached menstrual endometrial or stromal cells. Thus, endometriosis is a pseudo-pregnancy state and the corpus luteum produces progesterone to support and maintain the attached endometrial/stromal cells as if they were a fertilized egg. In most clinical cases at the time of diagnosis (2-6 months), the circulating as well as tissue levels of progesterone are too low to be detected and often misunderstood as progesterone resistance [10,11].

Another important factor in the context of the ideal profile of an antiprogestin for endometriosis is its effect on the endometrium [12]. The endometrium is under the well-balanced control of estrogens and progestins. Estrogens lead to a marked proliferation of the endometrium that might lead to endometrial hyperplasia if this effect is not controlled through the antiestrogenic effect of progestins. Sustained, persistent estrogenic stimulation in the absence of progestin ultimately results in hyperplasia. Our results point to the fact that the effect of estrogen is apparent only in the second phase of the disease (unpublished data), since the first wave of progesterone secretion by the corpus luteum to support the pseudo egg is sufficient to initiate the menstrual endometrial/stromal cell attachment on the peritoneal mesothelium. The treatment with a pure antiprogestin may therefore inhibit menstrual endometrial/stromal cell attachment on peritoneal mesothelium as well as the subsequent second wave of estrogen induced proliferation.

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RU 486 (Mifepristone) is the first and most widely studied antiprogestin. At present, it has been approved only for termination of second trimester pregnancies [13]. The long-term application of Mifepristone is hampered by its strong antiglucocorticoid effect [14]. A newer antiprogestin, CDB 4124, also known as Proellex®, was found to be 2.8 fold more potent than RU 486 without exhibiting any agonistic activity. The antiglucocorticoid activity was determined to be around one-third of that of Mifepristone [15]. The phase II clinical study evaluating the safety and efficacy of Proellex® (CDB-4124) in the treatment of premenopausal women with symptomatic endometriosis was discontinued due to adverse events (Clinical trials.gov; NCT00958412). There is an unmet need for a better understanding of the role of progesterone in the initiation and progression of endometriosis that will expand our knowledge to develop better antiprogestins for the safer treatment of endometriosis with minimal or no anti-glucocorticoid side effects.

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