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Progress in Clinical Studies of Progesterone: A Review

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Abstract

Progesterone, as the main steroid hormone, is secreted by the corpus luteum and plays an important role in the menstrual cycle, pregnancy maintenance, as well as pathogenesis analysis and treatment of many diseases. To systematically review the progress of progesterone in clinical research, this paper describes the physiological role and focuses on the impacts of progesterone on (1) pregnancy outcome, (2) perimenopause, menopause and debilitating period, and (3) the other diseases (such as endometriosis, endometrial cancer and breast cancer). Progesterone's widespread and critical role in the body has proven to be of constant clinical interest and it gives future perspectives on the potential of this hormone in clinical medicine.

Keywords: Progesterone; Physiological effects; Pregnancy; Perimenopause

Introduction

Progesterone is a 21-carbon steroid that belongs to hormones series called progestogens. It is secreted by the corpus luteum, and has a wide range of effects in the human body. Research on progesterone has a long history, but people still have not stopped studying it. According to statistics, women have an average menstrual cycle of 35 years in their lifetime, and each menstrual cycle contains a 14-day follicular phase and a 14-day luteal phase on average. In the early luteal phase of the menstrual cycle, progesterone is produced by the corpus luteum due to the stimulation of Luteinizing Hormone (LH). The progesterone production rate is about 1 mg/day during the follicular phase, and increases to 25 mg/day in the luteal phase [1-3].

As a type of female hormone (progestin), progesterone plays a vital role in pregnancy, perimenopause therapy and diseases research (Figure 1). As far as the establishment and maintenance of pregnancy are concerned, progesterone not only facilitates embryo implantation and provides a good pregnancy and immune environment, but also reduces the risk of miscarriage and premature delivery [4,5]. Moreover, modern assisted reproductive technology also requires the help of progesterone to increase the success rate of implantation [6]. For perimenopausal, menopausal and postmenopausal women, progesterone can be used as a Hormone Therapy (HT) component to participate in the treatment of cardiovascular disease, osteoporosis and others. In addition, progesterone also plays an important role in the pathogenesis analysis and treatment of some diseases, such as endometriosis, endometrial cancer and breast cancer [7-14].

This paper aims to outline the physiological effects of progesterone from three aspects: (1) the role of progesterone in pregnancy and childbirth (2) the treatment of progesterone in perimenopausal, menopausal and postmenopausal women and (3) the mechanism of progesterone in endometriosis, endometrial cancer and breast cancer.

Impact of Progesterone on Pregnancy Outcome

Preventing miscarriage: Progesterone plays an important role in the establishment and maintenance of pregnancy and can reduce the risk of miscarriage. Threatened miscarriage, a common gynecological emergency, is manifested by vaginal bleeding with or without abdominal pain. It can occur in 20% of pregnancies, and even deteriorates into spontaneous miscarriage for 20% to 25% of women [4]. According to some systematic reviews and meta-analysis, when women suffering from threatened miscarriage were treated with progesterone, the risk of miscarriage is reduced. Compared to women with low-risk pregnancies, women in the risk of threatened miscarriage have a lower serum progesterone level. When it progressed to spontaneous miscarriage, the serum progesterone content became lower and did not increase with gestation length [5]. Therefore, serum progesterone can be used as a serum biomarker to evaluate and prognosticate patients with threatened abortion [15]. A trial health technology assessment showed that women with the history of miscarriages

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are benefited from progesterone treatment. The study involved 4,153 women in UK who had early pregnancy vaginal bleeding. Women were randomly assigned to twice daily 400 mg progesterone vaginal suppositories or placebo. As a result, for the women who have had 3 or more miscarriages in the past, the live birth rate was 72% in the progesterone group and 57% in the placebo group [16].

Reducing the risk of preterm birth: Preterm birth is generally considered to be a syndrome caused by several pathological processes. For example, infections, vascular diseases and decidual degeneration, decreased progesterone action, and cervical diseases such as short cervix are all factors. The preterm birth can cause lifelong damage to neurodevelopmental function, and complications of preterm birth are the main cause of neonatal death [17-19]. The risk of preterm birth of twins is 8 to 9 times higher than that of singleton gestation. The preterm birth has become the most important factor affecting the morbidity and mortality of twins [20]. According to a meta-analysis, after the asymptomatic women with a twin gestation and short ultrasound cervix have taken the vaginal progesterone in the second trimester, the risk of preterm birth and neonatal morbidity and mortality are significantly reduced, with no deleterious effects on children's neurodevelopment [21]. Research in this area will help recommend vaginal progesterone to women with twin pregnancy and ultrasound short cervix to prevent preterm birth and improve perinatal outcomes. An updated meta-analysis of indirect comparisons shows that both vaginal progesterone and cervical resection can effectively prevent preterm birth. They are both effective in women with a singleton gestation, a history of spontaneous preterm birth and a short cervix [5].

Providing immune environment: Progesterone has the effect of mediating the immune system, which provides a suitable immune environment for embryo implantation and fetal development. In most cases, progesterone helps to establish an appropriate maternal response to fetal antigens and prevent the appearance of obvious inflammation [22]. When the body is exposed to harmless antigens, uterine Dendritic Cells (DCs) can initiate a powerful immune response to pathogens or guide the response to tolerance induction. Progesterone is beneficial to inducing semi-mature tolerogenic DCs to initiate tolerance induction and inhibits the pro-inflammatory response of mature DCs [23,24]. It also induces the Th2 dominant cytokine environment, and inhibits the pro-inflammatory immune response to promote maintenance pregnancy [22].

The effector/activated T cells cause pathological inflammation and the subsequent preterm birth and adverse neonatal outcomes can be treated by the anti-inflammatory effect of progesterone, that is, progesterone weakens the local pro-inflammatory response of the maternal-fetal interface and the cervix [25]. In addition, in the muscle layer tissue, it's believed that the progesterone signaling pathway hinders the production of pro-inflammatory cytokines, thereby suppressing the contractility of the muscle layer [26].

Assisting assisted reproductive technology: The first generation of *in vitro* Fertilization (IVF) technology, also known as *in vitro* Fertilization and Embryo Transfer technology (IVF-ET), can combine sperm and egg culture into a fertilized egg, which forms an embryo and then implants in the uterus to develop into a mature fetus. Embryo Quality (EQ) is an important factor affecting successful transplantation regarding this technology. In evaluating the efficacy of IVF-ET, the Cumulative Live Birth Rate (CLBR) is a key indicator [27]. It can optimize the connection between weeks, reduce patient shedding, and improve treatment efficiency. So CLBR has received continuous attention from the international academic community. With the widespread application of embryo freezing and resuscitation technology, the cumulative live birth rate is used as a new indicator to evaluate the effectiveness and safety of assisted reproductive technology. The recognition and application of the new indicator have continued to increase in recent years.

Studies have shown that the increase in serum progesterone in the late follicular phase reduces the utilization of embryos, thereby affecting the cumulative live birth rate [28]. The researchers measured different levels of progesterone in the serum of the test population and assessed the embryos eligible for transfer. The final results were presented in terms of embryo utilization and cumulative live birth rates. The comparison between groups showed that with the increase of serum progesterone levels, the levels of E2 and recovered oocytes rose as well, and the cumulative live birth rate of the low progesterone level group was significantly lower than that of the medium to high level group. There is also evidence that high levels of progesterone can bring better ovarian response [3], but it is related to lower embryo utilization and hinders the cumulative live birth rate. This finding indicates the possible impact of serum progesterone levels on IVF technology, which will help provide more information on the improvement of embryo utilization and cumulative live birth rates [28].

It's known that Frozen-thawed Embryo Transfer (FET) surgery is increasingly used in the treatment of infertility. It creates birth opportunities for women with genetic diseases or reproductive organ failure, which not only increases the cumulative pregnancy rate, but also reduces the risk of repeated pregnancy [29]. Progesterone can effectively coordinate the implanted embryo and the endometrial environment, increase the rate of live births, and reduce the rate of miscarriage [6]. To compare the effects of progesterone's administration on treatment, 3,013 women were divided into groups and were given intramuscular injections of progesterone and vaginal progesterone gel treatments in a study. The results show that supplementation of vaginal gel progesterone has a good effect on frozen-thawed embryo transfer, which can increase the implantation rate, delivery rate and live birth rate. This research is of great significance to increasing the success rate of freeze-thaw embryo inhibition [30]. However, when progesterone rises prematurely in the late follicular phase during the IVF cycle, it will have a negative impact on the implementation of assisted reproductive technology. Meanwhile, exposure of progesterone to divided estrogen drives the maturation of the endometrium. When progesterone rises prematurely, it will change endometrial gene expression patterns, leading to a more advanced secretory endometrial maturation, and decrease the pregnancy rate of *in vitro* fertilization [31].

Impact of Progesterone on Perimenopause, Menopause and Debilitating Period

Women's life cycle will go through five important stages: adolescence, premenopause, perimenopause, menopause, and debilitating period. In adolescence, women have the peak Bone Mineral Density (Peak BMD) [32,33] and then the balance of bone resorption and bone formation. The peak BMD remains stable, until the perimenopausal period begins to decline, and bone mass is gradually lost [34]. Both estrogen and progesterone play an important role in bone balance, that is, estrogen inhibits bone resorption, and progesterone promotes bone formation [35].

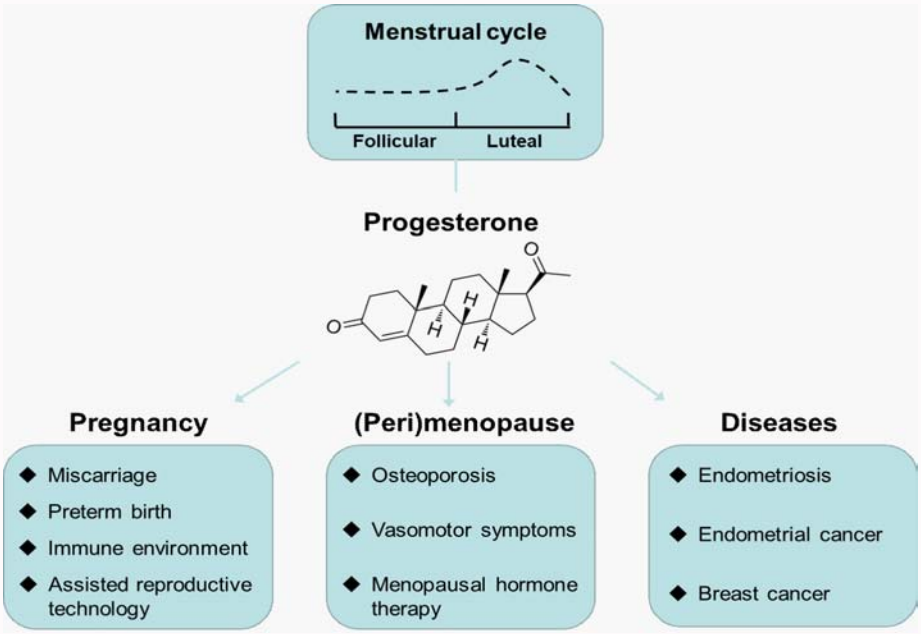

Figure 1: As a type of female hormone (progestin), progesterone plays a vital role in pregnancy, perimenopause therapy and diseases research.

In premenopause, at the beginning of a normal menstrual cycle, both the levels of estrogen and P4 are low. Then estrogen rises to the peak of 240%, which inhibits bone resorption, stimulates LH to form the peak, and triggers ovulation and luteinization. The follicular cells that produce estrogen begin to generate progesterone. When the progesterone content rises to the peak of 1,400%, the bone is formed due to stimulation [36]. Perimenopausal, a long transition period between premenopause and menopause, is characterized by significant hormonal changes. Perimenopausal hormone changes are manifested as high and unstable estrogen levels, low progesterone levels, and bone absorption greater than bone formation [34,37]. Therefore, the risk of osteoporosis in perimenopausal women is greatly increased. Especially, progesterone levels of elderly women entering menopause are reduced, which further causes bone loss. The level of BMD/bone strength in frail older women is related to the peak BMD and premenopausal loss [29]. Sclerostin is also an endogenous hormone that suppresses bone synthesis by inhibiting osteoblasts [38,39], and can be suppressed by estrogen. A three-month randomized, placebo-controlled clinical trial showed that oral progesterone does not affect serum sclerostin levels [33]. Therefore, the process that progesterone increases bone formation and sclerostin inhibits the bone metabolism, is independently regulated [40].

Women in menopause (1+ year past last menstruation) have typical symptoms such as hot flashes and Vasomotor Symptoms (VMS). The VMS, which refers to the heat dissipation response such as vasodilation and sweating caused by a sudden increase in core temperature, is related to visible changes in hormone content and usually lasts for a few minutes [41,42]. Various treatment methods have been tried to treat VMS, and it has been tested that progesterone is an effective drug for VMS [43,44]. In addition, hormonal changes during menopause will affect the central fat distribution and cause abdominal obesity, as well as high blood pressure [45-47]. Menopausal Hormone Therapy (MHT) is being used for menopausal women. MHT can be treated with estrogen alone, but more is a combination of estrogen and progesterone. However, many menopausal women refuse to receive MHT treatment because the results of the Women's Health Initiative (WHI) test on MHT indicate that MHT may cause more health risks, such as weight gain, breast cancer, venous thromboembolism, myocardial infarction, and stroke [44,48,49]. However, recent studies have proved that MHT is not the cause of the above diseases. For example, in a randomized, double-blind, placebo-controlled trial, 45 to 60 women randomly took transdermal estradiol plus intermittent micronized progesterone. The results show that TE+IMP has a tendency to improve cardiac autonomic control of healthy perimenopausal and early postmenopausal women, has a neutral or beneficial effect on cardiovascular disease, and prevents aging-related stress response and endothelial function change, and at the same time has a positive effect on women's depression. Therefore, even healthy women at the beginning of menopause can be benefited from the TE+IMP [48]. Meanwhile, data from a randomized, placebo-controlled, phase-3 supplementary trial showed that 40 to 65-year-old women who took daily estrogen/progesterone in the form of oral capsule TX-001HR had no weight gain and blood pressure increase clinically. This is an option for the treatment of moderate to severe VMS. This is because synthetic progesterone combined with hormone therapy can counteract the vasodilation effect of estrogen, while natural progesterone may have a positive effect on lowering blood pressure [49].

Impact of Progesterone on Other Diseases

Progesterone plays an important role in the pathogenesis analysis and treatment of many diseases. This part selects three gynecological diseases and comprehensively describes the pathogenic effects or treatments of progesterone in them. These diseases still plague many women, and we hope that by studying the status of progesterone in them, we can create possibilities for future breakthroughs in treatment options.

Endometriosis: Endometriosis, an inflammatory gynecological disease in which endometrial tissue is abnormally located outside the uterus, affects nearly 10% of women of childbearing age. The

main clinical symptoms are infertility and pelvic pain. According to histopathology and anatomical location, endometriosis is divided into three subtypes: Superficial endometriosis, deep invasive endometriosis and ovarian endometriosis symptoms of cysts [50-52]. Nowadays, the progesterone resistance hypothesis is considered to be one of the mechanisms of endometriosis, that is, the target tissue is less responsive to bioavailable progesterone. Because progesterone is a key hormone that mediates the endometrium and decidua, and exerts its effects through PRA and PRB [53,54], abnormal progesterone signals play an important role in the decidualization and establishment of ectopic endometrium. For women with endometriosis, homotopic endometrial cells cannot down-regulate genes required for decidualization, and the attenuation of progesterone target genes allows cells to grow and survive continually, leading to unlimited proliferation. At the same time, in patients with endometriosis, the expression of PRA increases, which leads to an abnormal increase in the ratio of PRA to PRB and therefore decreases progesterone responsiveness [7,8]. In addition, genetic factors such as progesterone receptor gene polymorphism and microRNA changes are important causes of progesterone tolerance. Inflammation, retrograde menstruation, and environmental toxins (dioxin) caused by abnormal progesterone signals can exacerbate progesterone tolerance [8]. Therefore, as possible therapeutic solutions, we could reduce the inflammatory stimulus of the endometrium to increase PR expression, and rebuild PR expression to restore progesterone responsiveness and therefore inhibit cell proliferation and stimulating shedding [7]. The progesterone resistance hypothesis is an important issue in the research of this disease, and further research is needed to understand it.

Endometrial cancer: Tending to occur in postmenopausal women, Endometrial Carcinoma (EC) is a major gynecological adenocarcinoma that arises from the endometrium [55-57]. Worldwide, EC is the sixth most common gynecological disease. It is the most common gynecological disease in the United States and Canada, and is second only to cervical cancer in China [58]. Estrogen can promote cell mitosis under the antagonism of other hormones, and drive the proliferation of endometrial epithelial cells through the endoplasmic reticulum, which leads to endometrial hyperplasia and potential EC. Progesterone is an indispensable hormone for maintaining eutrophic endometrium. It is beneficial to uterine implantation and also an effective estrogen antagonist, which can inhibit active cell division by reducing the expression level of endoplasmic reticulum. Progesterone also promotes the differentiation of endometrial glands and blood vessels. According to mouse model studies, in PR knockout mice, progesterone is not sensitive to the inhibitory effect of estrogen-induced endometrial hyperplasia, so it is inferred that the anti-proliferative effect of progesterone is mediated by PR [10,59].

At present, the standard care for the treatment of endometrial cancer is hysterectomy combined with bilateral salpingo-oophorectomy [60]. The prognosis of this method is satisfactory, but it will cause young patients to lose fertility [61]. Therefore, hormone therapies emerge, including oral Micronized Progesterone (MP) and "levonorgestrel Intrauterine Device (IUD)" in the uterus. The hormone therapy is less harmful to the body and can maintain the fertility of young EC patients [9]. Oral MP can protect the endometrium from estrogen, and the installation of an IUD has a strong progesterone release effect on the endometrium [10]. Some studies have shown that the levonorgestrel intrauterine device may be superior to oral progesterone in controlling endometrial cancer and complex atypical hyperplasia [11]. The effectiveness of this therapy for EC treatment is controversial, due to the insufficient analysis of the evidence of effectiveness research. Therefore, in order to control the condition of EC patients and reduce harm, larger-scale research is required for the hormone therapy [9,62].

Breast cancer: Breast cancer is the most common malignant tumor in women, which is highly related to estrogen, progesterone and their receptors [12,63]. In a normal body, estrogen and progesterone promote breast development during puberty in a paracrine manner. Estrogen plays a part in the initial stage of breast development. Progesterone is dependent on estrogen and is responsible for the cell proliferation of the breast through a synergistic effect [13,64]. Experimental studies on mice have shown that progesterone plays an extremely important role in inducing ductal side-branching of the mammary ducts, and affects alveolar development during pregnancy [13]. The selective knockout model in mice proves that PRB is the main mediator for progesterone to function and promote proliferation [65].

In order to study genetic variants related to urinary tract sex hormone levels and breast cancer risk, a study of premenopausal women was launched by Nichola Johnson [66]. The researchers performed a genome-wide association study on the samples, conducted additional analysis on the progesterone levels of a certain number of women, and did follow-up genotyping of 90,916 patients from the Breast Cancer Association Consortium and 89,893 control groups. The results of the study found that CYP3A7*1C alleles affect the metabolism of endogenous hormones, thereby reducing the risk of positive breast cancer in carriers. Therefore, for CYP3A7*1C carriers, reducing exposure to endogenous hormones before menopause can help prevent breast cancer.

In addition, estrogen has been the key research object of breast cancer risk for more than 50 years, but progesterone exposure is increasingly considered to be closely related to breast cancer related to hormone exposure. The data related to the high cell proliferation rate in the luteal phase of menstruation further proves this point [14]. Because of the unstable hormone levels of women after menopause and desperation, progesterone exposure will more easily because breast cancer risk. However, due to the obstruction of the periodic changes in serum progesterone levels and technical obstacles, there was no visible evidence of progesterone [67]. In a study of postmenopausal women, the correlation between circulating progesterone and progesterone metabolite levels and breast cancer risk was evaluated. The study analyzed 405 cases of breast cancer and 495 postmenopausal women with serum progesterone and progesterone metabolites quantitatively measured by a sensitive liquid chromatography-tandem mass spectrometry analysis. After 12 years of follow-up, the researchers found that at very low estradiol levels, higher progesterone levels are associated with lower breast cancer risk, and at higher estrogen levels, progesterone levels are associated with increased breast cancer risk. This result further proves that estradiol and progesterone are interdependent. The research also suggests that progesterone may affect the mitotic effect of breast cells through estradiol [68].

In short, the relationship between breast cancer risk and progesterone and other endogenous hormones needs to be studied on a larger scale, using highly sensitive detection methods. This improves menopausal hormone therapy and prevents the risk of breast cancer

that may be caused by progesterone exposure.

Conclusion and Future Perspectives

This paper summarized the physiological role of progesterone and its progress in clinical research. Studies have confirmed that progesterone plays an important role to establish and maintain pregnancy, reduce the risk of miscarriage and preterm birth, provide a suitable immune environment for embryo implantation and fetal development, and participate in assisted reproductive technology. In women's perimenopause, menopause and debilitating periods, progesterone is used as part of hormone therapy to help women improve physical and psychological abnormalities. In the treatment of endometriosis, endometrial cancer and breast cancer, the abnormal change of progesterone levels can be used as reference index and researchers can explore more possible mechanisms treatment breakthrough based on the mechanism of progesterone in these diseases. In conclusion, we expect more researchers to conduct further research on progesterone, so as to obtain a wider and more effective application in clinical practice.

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