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Effects of Different Forms of Progesterone on the threat of Spontaneous Pregnancy

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Abstract
This article discusses the effects of different forms of progesterone on the risk of miscarriage. Pregnancy involves a complex interplay between maternal neuro end ocrine and immunological systems in order to establish and sustain a growing fetus. Here we review research to date that focus on the pathways through which P4 mediates its actions on both the maternal reproductive and immune system. We will dissect the role of P4 as a modulator of inflammation, both systemic and intrinsic to the uterus, during human pregnancy and labor. The effects of different forms of progesterone on the risk of spontaneous abortion have also been analyzed.

Keywords: pregnancy, progesterone, PIBF, immune modulation, immune response, partial adrenal glands.

Introduction

Progesterone is a steroid hormone produced in the female body by the corpus luteum and partly by the adrenal glands. If the deficiency can put a pregnant woman at risk of miscarriage, then the excess is also not helpful, so it is necessary to control the level in the body of the future mother. "Progestin" is a general term for a substance that causes some or all of the biologic effects of progesterone. The term "progestin" is sometimes used to refer to the progesterone made in the laboratory that is in oral contraceptives and hormone replacement therapy. However, all progesterone and progestin products are made in the laboratory. The term "natural progesterone" is really a misnomer. "Natural progesterones," including the prescription products Crinone and Prometrium, are made from a chemical called diosgenin that is isolated from wild yam or soy. In the laboratory, diosgenin is converted to progesterone. The human body is not able to make progesterone from diosgenin, so eating wild yam or soy will not boost your progesterone levels.Over-the-counter (OTC) progesterone products may not contain progesterone concentrations as labeled. Also, topical progesterone products (preparations applied to the skin) marketed as cosmetics require no FDA approval prior to marketing. There is currently no limit on the amount of progesterone allowed in cosmetic products. In 1993 the FDA proposed a rule to limit the amount of progesterone in these products, but this rule was never finalized. Patients commonly take progesterone to help restart menstrual periods that unexpectedly stopped (amenorrhea), treat abnormal uterine bleeding associated with hormonal imbalance, and treat severe symptoms of premenstrual syndrome (PMS). Progesterone is also used in combination with the hormone estrogen to "oppose estrogen" as part of hormone replacement therapy. If estrogen is given without progesterone, estrogen increases the risk of uterine cancer.

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From the 3.5 month period, it is produced by the placenta. the pregnancy rate of progesterone is not the same and increases in proportion to the period.

The normative indicator varies within the following limits:

- up to 12 weeks - 9-47 USD / ml;
- After 28 weeks - 17-146 USD / ml;
- 29-40 weeks - 55-200 USD / ml.

Its presence is determined by a blood test.

It is not necessary to draw early conclusions based on a comparison of the actual presence of the hormone with standard indicators - decoding should be performed by a specialist. It is easy to upset the hormonal balance, but it is not easy to restore it.

Receptor-Mediated Actions

The organism is individual and the units of measurement are different, which makes comparison in principle impossible. With a lack of progesterone production by the body of the future mother, this drug is prescribed in the form of injections, tablets, suppositories.

Prescribing the hormone during pregnancy is justified only in cases where the uterus is well formed and there is a risk of miscarriage, there is a risk of placental abruption.

If an overdose occurs, it can lead to the following consequences:

- renal failure, manifested by edema;
- impaired liver function;
- headache, dizziness;
- increase in blood pressure;
- blood clots;
- problems with the gastrointestinal tract;
- sleep disturbances, depression;
- swelling and pain in the mammary glands;
- allergies with different appearances, etc.

In the slightest manifestation of an overdose, the treating physician should be notified for immediate action.

In early pregnancy Progesterone is produced by the corpus luteum whose duration has been estimated 12 ± 2 days. This organ is fundamental for pregnancy maintenance until the placenta (syncytiotrophoblast) takes over its function at 7-9th week of gestation, just after the expression of major histocompatiblity complex antigens is suppressed in extra-embryonic fetal tissue.

Progesterone is an essential hormone in the process of reproduction. Indeed, it induces secretory changes in the lining of the uterus and is essential for a successful implantation of the embryo. Moreover, Progesterone modulates the immune response of the mother to prevent rejection of the embryo, and enhances uterine quiescence and suppresses uterine contractions. Therefore it is theoretically plausible that P supplementation may reduce the risk of miscarriage in women with a history of recurrent miscarriages. Several studies have used Progesterone and related steroids

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(progestagens- Fig. 1) in the attempt to prevent spontaneous miscarriage and to increase the embryo implantation rates in assisted reproduction programmes. The term "progestagens" cover a group of molecules including both the natural female sex hormones Progesterone and 17-hydroxy Progesterone (17P) as well as several synthetic forms, all displaying the ability to bind Progesterone receptors.

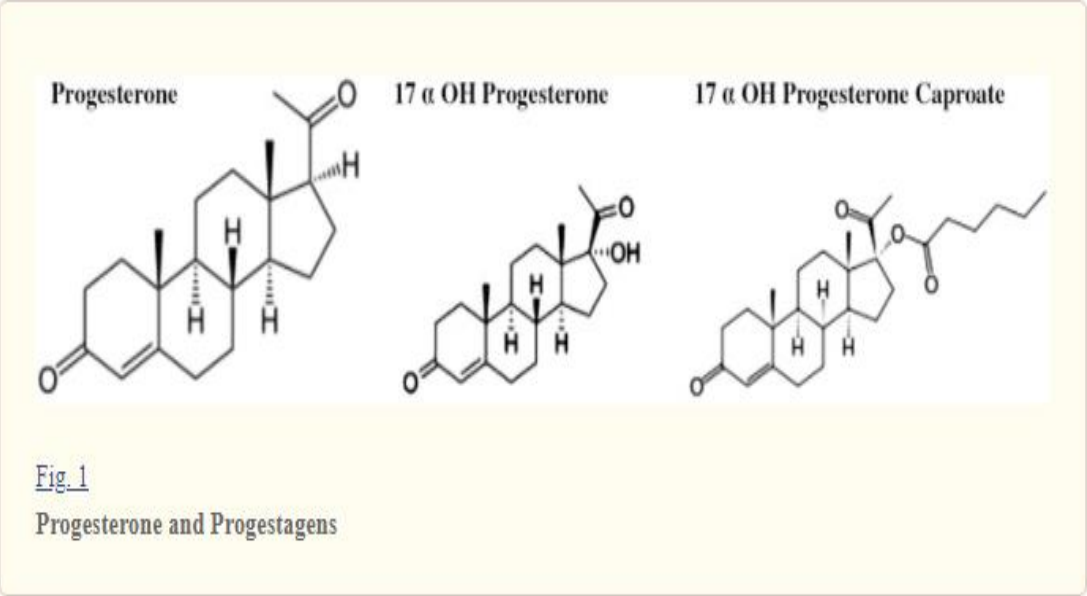

Fig. 1
Progesterone and Progestagens

Progesterone (Fig. 1) is a steroid hormone which plays a crucial role in each step of human pregnancy.

Although pharmacokinetics and pharmacodynamics features of progestagens have been studied, their use in human pregnancy remains controversial, i.e. the way of administration. Indeed, progestagens could be administered by three routes: orally, vaginally or intramuscularly. Oral administration guarantees optimal compliance by patients but shows many disadvantages; this route also results in side effects such as nausea, headache and sleepiness. The vaginal route results in higher concentrations in the uterus but does not reach high and constant blood levels. The drug administered intramuscularly occasionally induces non-septic abscesses, although it is the only route which results in optimal blood levels (Whitehead et al., 1990; Szabo and Szilagyi, 1996; Cunningham, 2001; Di Renzo et al., 2005; Christian et al., 2007). Several reports hypothesized an association between intrauterine exposure to progestagens in the first trimester of pregnancy and genital abnormalities in male and female fetuses. This was due to the possible up-regulation of androgen receptor operated by pharmacological doses of these steroids. However, maternal safety of progestagens has been reported in different trials. Neonatal safety has been evaluated in only one trial where mothers have been treated with 17 Progesterone. No effects of general health status, external genitalia, and psychomotor development have been reported at follow-up. Since the paucity of data, ongoing trials are encouraged to include the follow-up of neonates in their study design (Mosby, 2001).

The present paper aims to provide a comprehensive view of the literature on the effects of progestagens during early pregnancy. We describe the effects of progestagens for preventing recurrent miscarriages and managing threatened miscarriage.

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P4 Suppression of Pregnancy-associated Inflammation in Reproductive Tissue

Miscarriage is defined as pregnancy loss before 23 weeks' gestation, based on the first day of the last menstrual period. Miscarriage is associated with considerable physical and psychological morbidity, particularly in developing countries (World Health Organization, 1992). Haemorrhage into the decidua basalis and necrotic changes in the tissues adjacent to the bleeding usually accompany abortion; the ovum becomes detached and stimulates uterine contractions that result in expulsion (Cunningham, 2001).

Recurrent miscarriage has been defined as 3 or more consecutive episodes of spontaneous pregnancy losses with the same biological father (World Health Organization, 1992). Extensive investigation of women involved will fail to find a recognisable cause in up to half of the cases. Luteal phase defects, immunotolerance derangements, chromosomal anomalies and endocrine disorders are the most common recognisable causes. Accepting an independent risk of miscarriage to be 15%, a second loss could be calculated to occur at a rate of 2-3% while a third loss is expected in 0.34% of women.

Pregnant women have been shown to express mPRs and PGRMCs in T cells during pregnancy. P4-driven modulation of T cell receptor (TCR) signal transduction and T cell function are potentially mediated by membrane-bound PRs in human T cells. The downstream pathways following TCR engagement involves MAPK phosphorylation and inositol trisphosphate (IP3) production, the latter of which promotes the release of Ca^{2+} stored in the endoplasmic reticulum. On T cells, however, P4 binding to PGRMC1 and classical mPRs results in increased intracellular Ca^{2+} mobilization and reduced phosphorylation of ζ-chain-associated protein kinase 70 (Zap70) to modulate T cell activation and TCR-mediated immune responses (Figure 1). Both pathways modulate phosphorylation of transcription factors that include NF-κB, activator protein 1 (AP-1) and nuclear factor of activated T cells (NFAT), which are associated with pro-inflammatory gene expression as well as T cell activation and proliferation (Figure 1). If the analysis shows that the progesterone in the pregnant woman is high and exceeds the norms shown in the table, then there may be several reasons for this. Increased concentrations of the hormone are observed in pregnant women with twins or triplets. It is clear that there is no difference in the early days of pregnancy, but at 4 months of gestation (approximately 15-16 weeks) each fetus "occupies" its placenta and each placenta produces progesterone.

There is nothing strange about having more hormones in a woman's blood. Much depends on the period of the child, the increase in progesterone. For example, a slight increase in it at 5-6 weeks does not mean anything pathological, and high values at the end of the second and third trimesters may indicate that the placenta is maturing very slowly. An increase in progesterone may indicate the presence of tumors, neoplasms in the adrenal glands, ovaries, as well as with the formation of cysts. Abnormally high levels of progesterone in early pregnancy may be a sign of a hydatidiform mole. The term refers to abnormal past fertilization, in which grape-like cysts develop in the uterine cavity. This cluster grows rapidly, leading to a significant increase in progesterone levels.Proposed mechanisms of P4-regulated gene transcription to modulate T cell function. Classically, extranuclear nuclear P4 receptors (nPR) exist in an inactive state until P4 binding, after which it forms a dimer and translocates to the nucleus to bind to P4 response element (PRE) sequences within gene promoter regions to alter their transcriptional activity.

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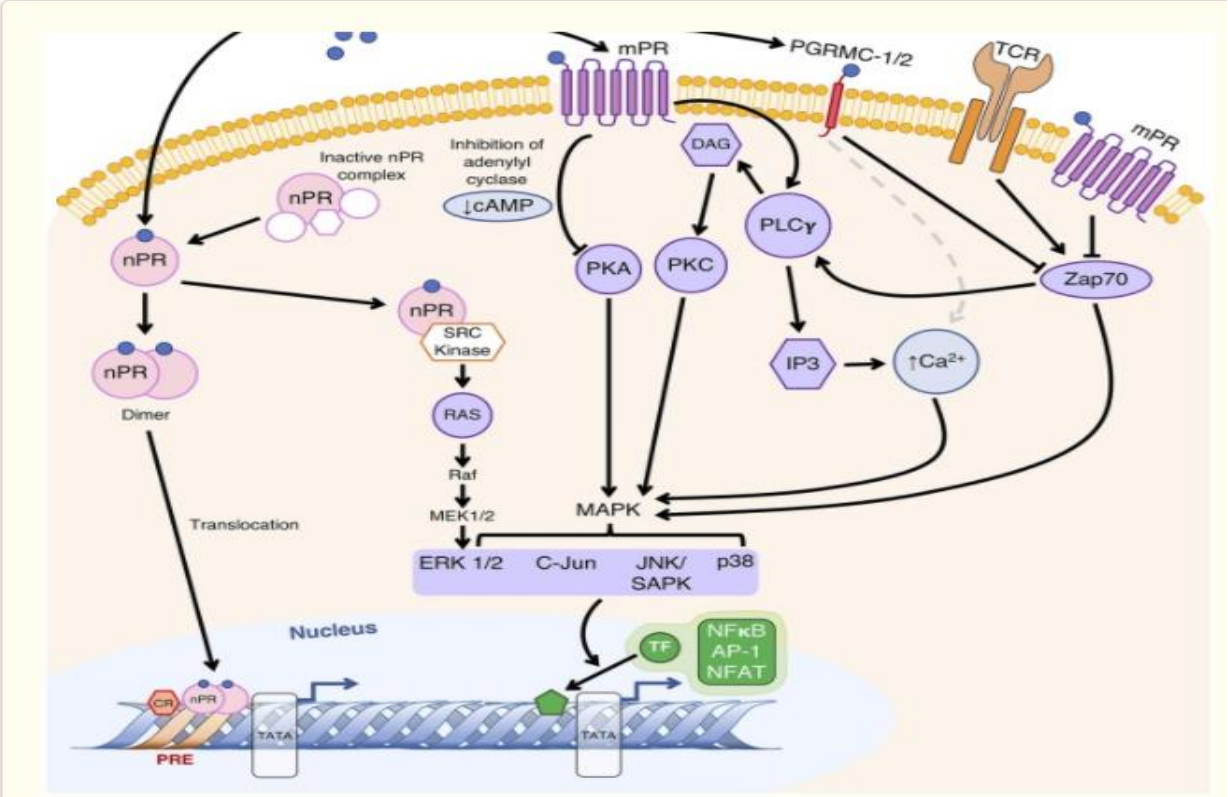

Alternatively, as a monomer, nPR-P4 acts *via* the Src kinase to activate the MAPK cascade. P4 bound to membrane P4 receptors (mPR) alters gene transcription regulated by second messengers (cAMP and Ca2+) and their associated extranuclear kinases (PKA and PKC) *via* the MAPK signal transduction cascade to result in phosphorylation of nuclear transcription factors (TF). Membrane-bound P4 receptors mPRs and P4 receptor membrane components (PGRMC) likely affect T cell receptor (TCR) signal transduction by modulating the activities of MAPKs through Zap70, as well as Ca2+ mobilization caused by phospholipase Cγ (PLCγ)-driven production of diacylglycerol (DAG) and 1,4,5-trisphosphate (IP3), which lead to modulation of pro-inflammatory gene expression and T cell activation *via* transcription factors NF-κB, AP-1 and NFAT. Adapted with permission from Mesiano et al., and Mani et al.

Conclusion

This occurs both systemically and locally at the maternal-fetal interface. Balanced interplay between the neuroendocrine and immune compartments is a key to establishing and regulating these crucial immunomodulatory changes during a healthy pregnancy. Functional P4 withdrawal occurs as a consequence of a predetermined gestational length, which can be altered by immune cell activity from the mother, the neonate or the maternal-fetal interface to drive the onset of labor. For most of pregnancy, P4 has to both suppress maternal responses to fetal antigens and prevent overt inflammatory responses to harmful environmental stimuli encountered by the mother. Disruption to P4 signaling that promotes the progression of pregnancy can lead to the mistiming of childbirth, which often bears adverse consequences for the health of both the mother and fetus. The design of novel effective therapies for obstetric complications will be dependent on future research that further elucidates the mechanistic details of the P4 signaling network, specifically with regards to interactions between the immune and reproductive systems that occur during both healthy and pathological pregnancies.

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