Section A -Research paper

Uses of Progesterone in Prevention of Preterm Labour in Patients with History of Spontaneous Preterm Delivery and Short Cervix

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Abstract:

Progesterone is an essential hormone in the process of reproduction. It is involved in the menstrual cycle, implantation and is essential for pregnancy maintenance. Although the pharmacokinetics and pharmacodynamics of progesterone have been well studied, and since 1935 it has been synthesised and is now available commercially, its use in the pathophysiology of pregnancy remains controversial. One of these concerns is the way in which the hormone is administered, with parenteral use proving the best way to obtain optimal plasma levels. Another concern is the paucity of randomised controlled trials and the different dosages and populations studied. As a result, the therapeutic application of progesterone in pregnancy is restricted to the prevention and treatment of threatened miscarriage, recurrent miscarriage and preterm birth. Progesterone is efficacious when continuation of pregnancy is hampered by immunological factors, luteinic and neuroendocrine deficiencies and myometrial hypercontractility. This may explain the reduction in the incidence of preterm birth in high risk pregnant women using high-dosage prophylactic progesterone.

Keywords: progesterone, Preterm Labour.

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Introduction:

Progesterone also known as P_4 (pregn-4-ene-3,20-dione) is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen **(1).**

In mammals, progesterone, like all other steroid hormones, is synthesized from pregnenolone, which in turn is derived from cholesterol (figure 1). Cholesterol undergoes double oxidation to produce 20, 22-dihydroxycholesterol. This vicinal diol is then further oxidized with loss of the side chain starting at position C-22 to produce pregnenolone. This reaction is catalyzed by cytochrome P450scc. The conversion of pregnenolone to progesterone takes place in two steps. First, the 3-hydroxyl group is oxidized to a keto group and second, the double bond is moved to C-4, from C-5 through a keto/enol tautomerization

reaction. This reaction is catalyzed by 3beta-hydroxysteroid dehydrogenase / delta (5)-delta(4)isomerase **(2)**.

Progesterone in turn is the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, estrone and estradiol. Pregenolone and progesterone can also be synthesized by yeast **(3).**

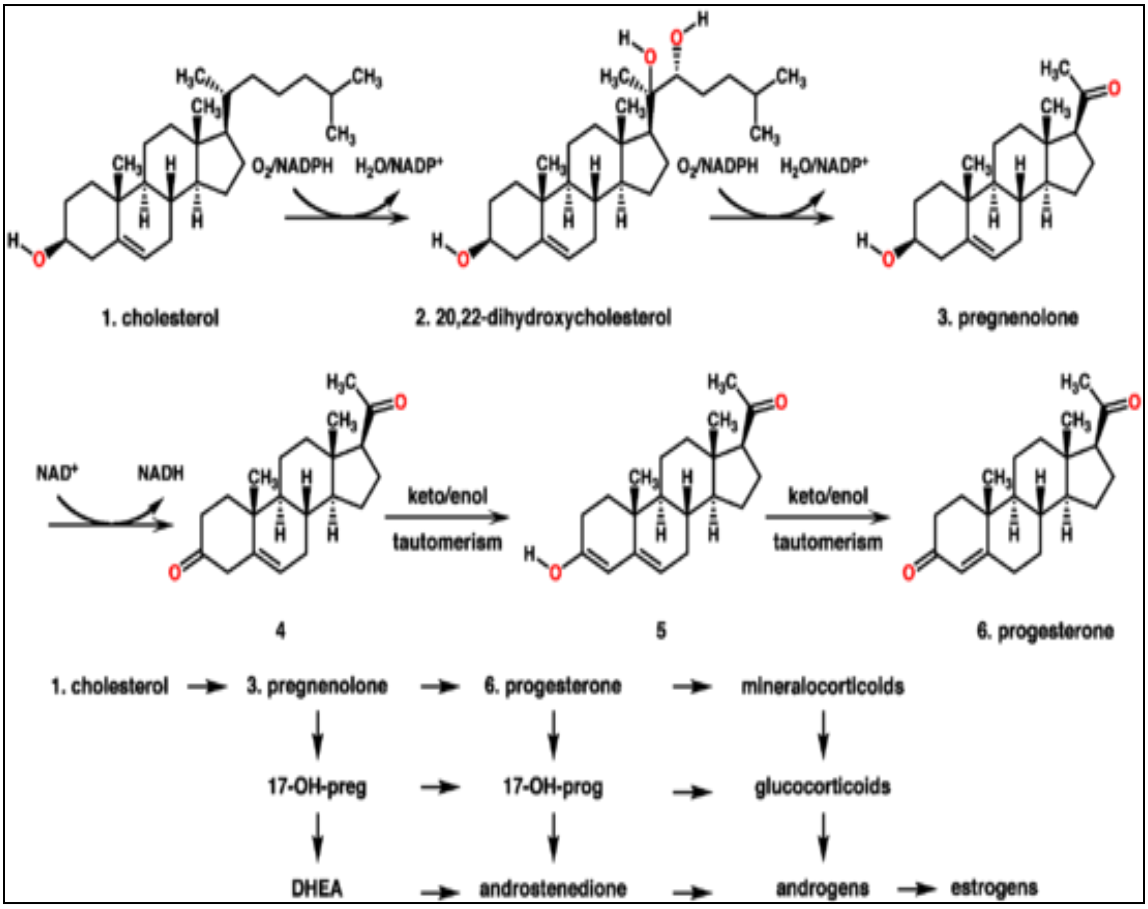

Figure (1): Top: Conversion of cholesterol *(1)* into pregnenolone *(3)* to progesterone *(6)*. **Bottom:** Progesterone is important for aldosterone (mineralocorticoid) synthesis, as 17-hydroxyprogesterone is for cortisol (glucocorticoid), and androstenedione for sex steroids.

Effect of progesterone on Reproductive system:

Progesterone is sometimes called the "hormone of pregnancy", and it has many roles relating to the development of the fetus:

- Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus, making it thick and impenetrable to sperm. If

pregnancy does not occur, progesterone levels will decrease, leading, in the human, to menstruation. Normal menstrual bleeding is progesterone-withdrawal bleeding. If ovulation does not occur and the corpus luteum does not develop, levels of progesterone may be low, leading to anovulatory dysfunctional uterine bleeding.

- During implantation and gestation, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy.
- Progesterone decreases contractility of the uterine smooth muscle.
- In addition, progesterone inhibits lactation during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production.
- A drop in progesterone levels is possibly one step that facilitates the onset of labor.**(4)**

Progesterone is important for pregnancy maintenance Progesterone production by the corpus luteum is essential for the establishment of pregnancy and for its maintenance in the first 8 weeks of gestation in women, Afterwards progesterone production is of placental origin and there is no evidence of progesterone withdrawal before term or preterm labour **(5).**

Progesterone is the predominant pregnancy hormone and has a suppressive action on pre-labour genes, it decreases uterine sensitivity to oxytocin, probably via a direct effect on the oxytocin receptor. In addition, progesterone exerts an inhibitory effect on prostaglandin activity via an effect on prostaglandin dehydrogenase (the main enzyme responsible for inactivation and metabolism of prostaglandins). The overall inhibitory effects of progesterone on pre-labour factors allows enlargement of the uterus without increasing uterine contractility. For many years it has been known that progesterone withdrawal is the stimulus for labour in many animal models. In humans, a functional withdrawal of progesterone is likely to be integral to the onset of labour and administration of exogenous progesterone may be beneficial in preventing preterm labour **(6).**

Progesterone is considered important for pregnancy maintenance in humans because inhibition of progesterone action could result in labour **(7).**

Adverse effects:

Progesterone may entail various systemic side effects such as mood swings, headache, dyspepsia, abdominal pain, constipation, diarrhea, nausea, vomiting, depression, loss of libido, dyspareunia, drowsiness, breast pain, urinary frequency, fatigue, dizziness, genital itching, back pain, fever, flu-like symptoms, and sleep disorders **(8).**

Medical applications:

The use of progesterone and its analogues have many medical applications, both to address acute situations and to address the long-term decline of natural progesterone levels. Because of the poor bioavailability of progesterone when taken orally, many synthetic progestins have been

designed with improved oral bioavailability**(5).**

Dodd et al., (9) reported that administration of progesterone was associated with reduced risks for preterm delivery before 37 weeks of gestation Moreover, treatment with progesterone was associated with lower risks for birth weight below 2500 g.

Care et al., (10) published a randomized, double- blind, placebo-controlled trial of vaginal progesterone versus placebo in decreasing the rate of spontaneous preterm birth. The trial included patients with at least one previous spontaneous preterm birth, a prophylactic cervical cerclage, or a uterine malformation (n-142). Patients were allocated to receive either daily progesterone (100 mg) or placebo by vaginal suppository from 24 to 34 weeks of gestation. The rates of preterm delivery at both less than 37 weeks and less than 34 weeks were lower in the progesterone group than in the placebo group.

Randomized clinical trials indicate that progesterone administration to women with a history of a previous preterm birth reduces the rate of spontaneous preterm birth **(11).**

Weekly injections of 17 - hydroxyprogesterone starting in early mid-trimester have been shown to be effective in reducing the rate of preterm birth in women with a prior spontaneous preterm birth **(12).**

Administration of progesterone during the late second and third trimesters, to women with a previous preterm birth, will significantly reduce the risk of a recurrent preterm birth. Progesterone currently the only agents that can be considered for use during pregnancy since, besides the required progestogenic effects, they do not have androgenic, antiandrogenic or oestrogenic properties **(13).**

Specific uses of progesterone:

a. In-Vitro Fertilization (IVF):

Progesterone is used to support pregnancy in Assisted Reproductive Technology (ART) cycles such as In-Vitro Fertilization (IVF). While daily intramuscular injections of Progesterone-In-Oil (PIO) have been the standard route of administration, A recent meta-analysis showed that the intravaginal route with an appropriate dose and dosing frequency is equivalent to daily intramuscular injections(**14).**

In addition, a recent case-matched study comparing vaginal progesterone with PIO injections showed that live birth rates were nearly identical with both methods**(15).**

b. Recurrent pregnancy loss:

Patients with recurrent pregnancy loss due to inadequate progesterone production may receive progesterone **(16).**

c. Non-pregnant women:

Progesterone is also used in non pregnant women with a delayed menstruation of one or more weeks, in order to allow the thickened endometrial lining to slough off. This process is termed a progesterone withdrawal bleeding. Progesterone is taken orally for a short time (usually one week), after which the progesterone is discontinued and bleeding should occur **(17).**

d. Role in preterm labour:

Women with a short cervix in the trial had benefit in two ways: a reduction in births less than 32 weeks and a reduction in both the frequency and the time their babies were in intensive care **(18).**

Vaginal progesterone was shown to be better than placebo in reducing preterm birth prior to 34 weeks in women with an extremely short cervix **(11).**

The administration of vaginal progesterone significantly reduced the risk of preterm birth occurring at <28 to <35 gestational weeks, as well as respiratory distress syndrome (RDS), composite neonatal morbidity and mortality, birth weight <1500 g and admission to the neonatal intensive care unit (NICU) (**19).**

Conde-Agudelo & Romero (20) suggested that vaginal progesterone could prevent preterm birth in women with a history of preterm birth.

According to **Di Renzo et al., (13),** women with a short cervix that received hormonal treatment with a progesterone gel had reduced risk of preterm birth. The hormone treatment was administered vaginally every day during the second half of a pregnancy.

Two new multisite randomized double-blind trials addressed the efficacy of progesterone in women at increased risk for preterm labor:

1- In the first study, 655 women with twin gestations received weekly intramuscular injections of 17P or placebo beginning at 16 to 20 weeks of gestation and ending at 35 weeks. Delivery or fetal death before 35 weeks was not significantly different in the two groups **(21).**

2- In the second study, 413 women with cervical length of 15 mm or less on transvaginal sonography examination at 20 and 25 weeks of gestation received either vaginal progesterone or placebo from 24 to 34 weeks of gestation. Significantly, fewer women in the progesterone group than in the placebo group had a spontaneous birth before 34 weeks (19.2% versus 34.4%). However, no significant difference was observed in neonatal morbidity **(22).**

Progesterone treatment reduced the number of uterine contractions and significally reduced preterm delivery rates. This means that, while some women still delivered prematurely, progesterone treatment helped more- high risk women carry their pregnancies longer than aplacebo treatment vaginal progesterone suppositories have been shown to decrease the rate of preterm birth in patients **(23)**.

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