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Dydrogesterone and pre-term birth

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Abstract: Progestin supplementation appears to be a promising approach to both preventing initiation of pre-term labor and treating it once it is already established. Successful pregnancy depends on maternal tolerance of the fetal "semi-allograft". A protein called progesterone-induced blocking factor (PIBF), by inducing a Th2 dominant cytokine production mediates the immunological effects of progesterone. Over time, various attempts have been made to clarify the question, whether progestogens can contribute positively to either prevention or treatment of pre-term labor and birth. Dydrogesterone treatment of women at risk of pre-term delivery results in increased PIBF production and IL-10 concentrations, and lower concentrations of IFNγ and could be effective for prevention or treatment of pre-term labor. Further randomized studies are needed.

Keywords: dydrogesterone; pre-term birth; progesterone-induced blocking factor.

Introduction

Pre-term birth is defined as delivery before 37th week of pregnancy. Although pre-term births appear to have plateaued over the past 3 years [1], it still remains a major public health problem. It is a central problem in obstetrics, and the most important risk factor for perinatal morbidity and mortality [2]. Although medical interventions have been successful at improving neonatal outcomes in premature infants, strategies to prevent pre-term birth, by preventing or halting pre-term labor, have been largely unsuccessful [3]. The problem of pre-term births involves the different continents and ethnicities. In 2005, there were an estimated 12.9 million pre-term births, representing about 10% of all births worldwide [4]. Pre-term births have a major impact on economy. Estimates from the National Center for Health Statistics in the USA from 2005 suggest that the total cost for care of premature infants was in excess of 26.2 billion dollars annually, that was 10 times higher than for the term-born infants [5].

Progesterone-induced blocking factor (PIBF)

Theoretical knowledge of the causes of premature birth has progressed over the past 30 years, but the identification of the cause in each case is very difficult, and sometimes impossible. Some unexplained pre-term deliveries might be attributable to a deleterious immune response of the mother toward the fetus [6]. Allogeneic stimulation occurring during pregnancy allows the binding of progesterone to specific lymphocyte-expressed receptors [7]. Many of the effects of progesterone are mediated by a lymphocyte-derived protein PIBF. PIBF has several antiabortive effects in vivo and appears to be the pivotal mediator in progesterone-dependent immunomodulation [8]. During normal uneventful pregnancy the concentration of PIBF continuously increases from the 7th to the 37th gestational weeks. After the 41st week of pregnancy, PIBF concentrations dramatically decrease. In patients with diagnosis of threatened pre-term delivery PIBF levels fail to increase during pregnancy [9].

Progesterone-induced blocking factor and arachidonic acid

It is known that prostaglandins play an important role for the mechanism of labor. The first step from prostaglandin synthesis to arachidonic acid is regulated by cyclooxygenase [8]. PIBF inhibits arachidonic acid release by a direct

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action on the phospholipase A2 enzyme [10, 11]. Its immunological effects include inhibition of NK activity and an action on the cytokine balance [7, 12]. PIBF inhibits the synthesis of prostaglandin F2 α, and the above effects are abrogated in the presence of exogenous arachidonic acid, suggesting that PIBF interferes with either the release or the action of arachidonic acid [10]. Indeed, PIBF inhibits phospholipase A2, which is required for arachidonic acid liberation, thus PIBF reduces the availability of the precursor for PG synthesis [13]. The lack of prostaglandins besides reducing the contractility of the uterine smooth muscle also inhibits the production of IL-12 (a cytokine which stimulates NK activity) and results in a lowered cytotoxic NK activity [11]. Prostaglandin F2 α has been shown to cause a significant increase of peripheral NK activity in vitro and this effect was corrected by progesterone [14]. Originally high progesterone sensitivity of pregnancy lymphocytes decreased while low sensitivity to prostaglandin E2 increased during labor. Except for prostaglandin E2 sensitivity all parameters of the lymphocytes obtained from women with threatened pre-term delivery were similar to those of lymphocytes obtained during labor [15].

The effects of PIBF on NK and cytokine activity

PIBF plays a role in the maintenance of pregnancy, most likely by inhibiting NK lymphocytes. Neutralization of endogenous PIBF activity in pregnant mice by anti-PIBF antibody results in a 70% reduction in the number of viable fetuses, and this is associated with an increased splenic NK activity. Ninety percent of pregnancy loss induced by anti-PIBF administration is corrected by treatment of the pregnant animals with anti-NK antibodies [16]. These data suggest that, at least in mice, PIBF contributes to the success of pregnancy and that the major part of its pregnancy-protective effect is due to its NK inhibitory activity [17].

The second main mechanism of action of PIBF during pregnancy is the induction of Th_2 dominant cytokine response [18]. The secreted PIBF facilitates the production of IL-3, IL-4, and IL-10, while it suppresses Th_1-cytokines, such as IL-12 and IFNγ both in vitro and in vivo [18–20]. In our study we found that the concentration of IL-10 was significantly lower, whereas serum levels of IL-6 and IFNγ were higher in women with preterm birth, than in healthy pregnant women involved in control group [18].

Progestogen treatment (dydrogesterone) in pre-term labor and delivery

Prevention and treatment of pre-term birth is therefore a major goal in obstetric care. There is increasing evidence that progestogen treatment reduces the rate of pre-term delivery. The mechanism of protection could be a combination of an immunological effect and the action of progesterone on the myometrium [21]. Over time various attempts have been made to clarify the question, whether progestogens can contribute positively to either prevention or treatment of pre-term labor and birth. Only certain progestogens can be considered for use in pregnancy (progesterone, dydrogesterone and 17α-hydroxy-progesterone-caproate [22–24].

Recent studies suggest that progestogens can be considered the treatment of choice for preventing pre-term labor [21]. Progesterone plays a role in the maintenance of uterine quiescence during pregnancy. It has been shown to possess a tocolytic action on the myometrium [22], partly by inhibiting gap junction formation. Gap junctions permit intercellular passage between the smooth muscle cells [25]. Labor is associated with an increasing number of gap junctions, and this increase is regulated by estrogen, progesterone, and prostaglandins [26].

Prostaglandins increase during parturition and stimulate myometrial contractility. Progesterone prevents prostaglandin F2 α synthesis and release, thereby promoting uterine quiescence [21].

We found so far two published studies about dydrogesterone in prevention or treatment of pre-term birth. In our study we showed effective treatment with dydrogesterone when pre-term labor has already started in patients with intact membranes. Our data suggest that treatment of women at risk of pre-term delivery with dydrogesterone at higher dose results in increased PIBF production and IL-10 concentrations, and lower concentrations of IFNγ [6]. According to experience of another author dydrogesterone at lower dose could be effective for prevention or treatment of pre-term labor [22]. To clarify this point, further randomized studies are needed.

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