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Progesterone and threatened abortion: a randomized clinical trial on endocervical cytokine concentrations

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ABSTRACT

The purpose of this study was to investigate the effect of vaginal progesterone on endocervical cytokine concentration in women at risk of threatened abortion. One hundred and sixty pregnant women with clinical symptoms of threatened abortion before the 20th week of pregnancy were randomly assigned to receive vaginal progesterone or placebo. Cervical fluids were collected and endocervical concentrations of different cytokines (IFNγ, TNFα, IL-8, IL-10 and IL-12) were analyzed before and one week after progesterone or placebo treatment. A significant decrease in IFNγ and increase in IL-10 in endocervical fluid was seen when the values were compared before and after progesterone treatment. However, there were no significant differences in pregnancy outcomes between the placebo and progesterone groups. We conclude that despite the failure of vaginal progesterone treatment to improve pregnancy outcomes, progesterone can induce a shift in the concentration of cytokines in endocervical secretions.

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1. Introduction

Threatened abortion is defined as vaginal bleeding during pregnancy, while the cervix is closed. This condition is often accompanied by increased uterine contractility (i.e. cramping) and cervical dilatation. In a fraction of cases, a threatened abortion may lead to a spontaneous abortion (15–20% of cases). A threatened abortion can be caused by multiple pathologies, but the etiology in the majority of cases is unknown. Causes of threatened abortion in the first trimester of pregnancy include chromosomal anomalies, Mullerian anomalies, maternal infections, and other environmental exposures such as smoking and caffeine intake (De la Rochebrochard and Thonneau, 2002). Further investigation has revealed that the stress response cascade triggered by immune activation due to the disequilibrium of the endogenous microflora not only deepens the threat to pregnancy maintenance, but also impedes fetomaternal tolerance (Friebe and Arck, 2008). On the other hand, inadequate immunological tolerance between mother and fetus has been suggested to be a probable etiology of threatened abortion. There is emerging evidence that dysregulation of the immune response may be associated with spontaneous abortion in the first trimester of pregnancy (Wegmann et al., 1993).

A considerable body of evidence shows that a shift from T-helper 2 (Th2)-dependent anti-inflammatory cytokines to T-helper 1 (Th1)-mediated production of pro-inflammatory cytokines is a characteristic feature of aborted pregnancy. This view is supported by studies that have indicated an association between Th1-mediated immune responses and reproductive failure (Wegmann et al., 1993; Paradisi et al., 2003). Moreover,

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anti-inflammatory cytokines may be important in preventing spontaneous abortion (Paradisi et al., 2003).

Tumor necrosis factor α (TNFα) is a Th1-dependent pro-inflammatory cytokine that provokes cytotoxic activity and leads to trophoblast apoptosis (Curry et al., 2007; Wilke et al., 2006; King et al., 1996). A Th1-dependent increase in the production of IL-12 and a decrease in the expression of IL-10, an anti-inflammatory cytokine, activate maternal lymphocytes and result in pregnancy failure (Yui et al., 1994). It has been reported that a high level of IL-10 production provides protection for pregnancy (Yui et al., 1994). Interestingly IFNγ, a pro-inflammatory Th1-dependent cytokine, is increased in concentration in placentas of aborted pregnancies, whereas IL-10 is the dominant cytokine in low abortion populations (Hayakawa et al., 1999).

Progesterone is well known as a mediator that is required for successful implantation of a fertilized ovum and maintenance of pregnancy (Tangri and Raghupathy, 1993). Human chorionic gonadotropin (hCG) stimulates production of progesterone from the corpus luteum during early pregnancy (Graham and Clarke, 1997). It has been proposed that inadequate secretion of progesterone during the luteal phase might be an important cause of miscarriage during the early weeks of pregnancy. Progesterone facilitates the process of implantation and maintenance of pregnancy by inhibiting myometrial contractions and stabilizing the endometrium (Di Renzo et al., 2005). Interestingly, an immunomodulatory role for progesterone has been proposed (Yui et al., 1994). Progesterone, a sex-steroid hormone and a key factor in the successful implantation and maintenance of pregnancy, also induces progesterone-induced blocking factor (PIBF), which promotes a shift from Th1-dependent cytokines toward Th2-dependent cytokines and supports pregnancy (Simoncini et al., 2006).

Previous studies have investigated the influence of progesterone on blood cytokine concentrations in women with threatened abortion (Simoncini et al., 2006). However, to the best of our knowledge, there are no studies concerning the impact of progesterone on endocervical concentrations of cytokines in women with threatened abortion. Moreover, progesterone has been recently recognized to be an effective hormone for the prevention of preterm birth. A randomized clinical trial investigating the effect of vaginal progesterone gel in women with a short cervix on ultrasound revealed a 45% reduction in the rate of preterm birth with improved neonatal outcome. They postulated that this effect was mediated by preventing preterm birth associated with infection (Walch and Huber, 2008).

We decided to survey the effects of progesterone on endocervical concentrations of cytokines in a group of women with threatened abortion in a randomized placebo-controlled double-blinded clinical trial and compare the pregnancy outcomes based on the treatment regimen.

2. Materials and methods

2.1. Study design and participants

A randomized double-blind placebo-controlled parallel-group clinical trial was performed between June 2006 and May 2011 in the obstetrics and gynecology ward of Vali-e-Asr teaching hospital in Tehran (IRCT registration number: IRCT201012035294N1). The study was approved by the Ethics Committee of the Medical University of Tehran and carried out in accordance with good clinical practice and the Declaration of Helsinki (Decision no: 1-3-10-5-25-12). A total of 160 eligible patients were allocated randomly into two groups. One of the groups received progesterone treatment and the other received placebo. The inclusion criteria were presence of clinical symptoms of threatened abortion (bleeding, spotting, and uterine cramps before the 20th week of pregnancy) and singleton pregnancy.

Women with systemic diseases, maternal hypertension before or during pregnancy, uterine tenderness, genetic or anatomical defects of the fetus, renal or cardiac diseases, genital tract anomalies of the mother and diabetes and those patients who had used a progestational drug during pregnancy, prior to being recruited into the study, were excluded (Hassan et al., 2011).

The treatment group received a vaginal suppository containing 200 mg of progesterone twice a day for one week. The placebo group received a placebo suppository twice a day for the same period of time. General and obstetric examinations with vaginal ultrasound were carried out on admission in all of the patients. This vaginal ultrasound was performed to exclude patients with multiple gestation or fetal anomalies and to estimate the exact gestational age. Serial vaginal ultrasounds were performed after patients started the treatment and at 20 weeks of gestation. All of the patients included in our study had proper access to routine hospital care.

Swab samples of endocervical secretion were prepared during the primary examination for both groups and the second sampling was done at the end of therapy. Samples of endocervical secretion were collected with Dacron swabs, stored at −70 °C, and transferred to the laboratory at −20 °C within 1–2 h (Kalinka and Radwan, 2006).

A simple questionnaire was used to gather data pertaining to the demographic characteristics and medical history of each subject. The follow-up visits were made until the time of delivery. After the end of the study all data were gathered at the gynecology ward of the hospital. We obtained written informed consent from all the participants in our study.

A computer-generated sequence with a block size of four was utilized to randomly allocate each participant to the treatment or placebo groups. Sequential numbers were given to the patients and their assigned numbers were sent to a research assistant who was the only one with access to the randomization list. The investigators were given prepared treatments in numbered envelopes and the participants received the treatments according to their assigned numbers twice daily for one week. Neither the patients nor the investigators who recruited them were aware whether they were using the placebo or the treatment until the study was complete. The investigators retained the number for each patient until the end of the study.

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