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The effect of progesterone supplementation on pregnancy rates in controlled ovarian stimulation and intrauterine insemination cycles: a randomized prospective trial☆

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ABSTRACT

Objective: To evaluate the effect of vaginal progesterone as luteal phase support on pregnancy rates in controlled ovarian stimulation and intrauterine insemination cycles in couples with unexplained or mild male factor infertility.

Study design: 290 Patients who met the inclusion criteria were included in a prospective randomized controlled trial. All patients underwent controlled ovarian stimulation and intrauterine insemination: 148 patients were randomized to start with a supported cycle and 142 patients with an unsupported cycle. In supported cycles, patients received vaginal progesterone once daily from the day after insemination until 12 weeks of pregnancy or, in non-pregnant women, for 14 days. No progesterone was given during unsupported cycles. The main outcome measures were clinical pregnancy rates per cycle.

Results: In total, 148 cycles with luteal phase support and 142 cycles without luteal phase support were performed. The clinical pregnancy rates per cycle were higher for cycles with luteal phase support than for the unsupported cycles (24.3% vs. 14.1% respectively, $p = 0.027$).

Conclusion: The use of vaginal suppositories as luteal phase support significantly improved clinical pregnancy rates in controlled ovarian stimulation and intrauterine insemination in patients with unexplained or mild male factor infertility.

1. Introduction

Progesterone is an important factor that is necessary for successful implantation and continuation of pregnancy [1]. Mifepristone as a progesterone antagonist interferes with progesterone receptors in the endometrium and induces termination of early pregnancy [2]. In the absence of progesterone, implantation will be impaired and pregnancy cannot occur. Progesterone induces secretary changes in endometrium, so endometrial receptivity will be improved [3].

To achieve an optimal luteal phase, progesterone levels should be adequate. Progesterone is secreted by the corpus luteum, which is dependent on luteinizing hormone (LH). Pulsatory secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus regulates LH, so using GnRH agonists and antagonists in assisted reproductive technology (ART) cycles leads to luteal phase deficiency with low progesterone levels. In cycles of controlled ovarian stimulation with intrauterine insemination (IUI), growth of multiple follicles occurs and high levels of sex steroids produced by multiple corpora lutea may reduce LH secretion and shorten luteal phase duration [4]. Olson et al. reported luteal phase deficiency in 20% of cycles stimulated by human menopausal gonadotropins, and a beneficial effect of using human chorionic gonadotropin (hCG) in this situation [5] (Fig. 1).

For many years progesterone has been used as luteal phase support in ovulation stimulation. Although its usefulness in the luteal phase has been proven in ART [6,7], there is controversy about the benefit of progesterone in controlled ovarian stimulation (COS) and IUI cycles [8–10]. The aim of the present study was to evaluate the effect of luteal phase vaginal progesterone supplementation on pregnancy rates in women with unexplained infertility or mild male factor that were treated by ovarian stimulation and IUI.

2. Materials and methods

From April 2009 to November 2010, 290 couples with unexplained infertility or mild male factor infertility completed

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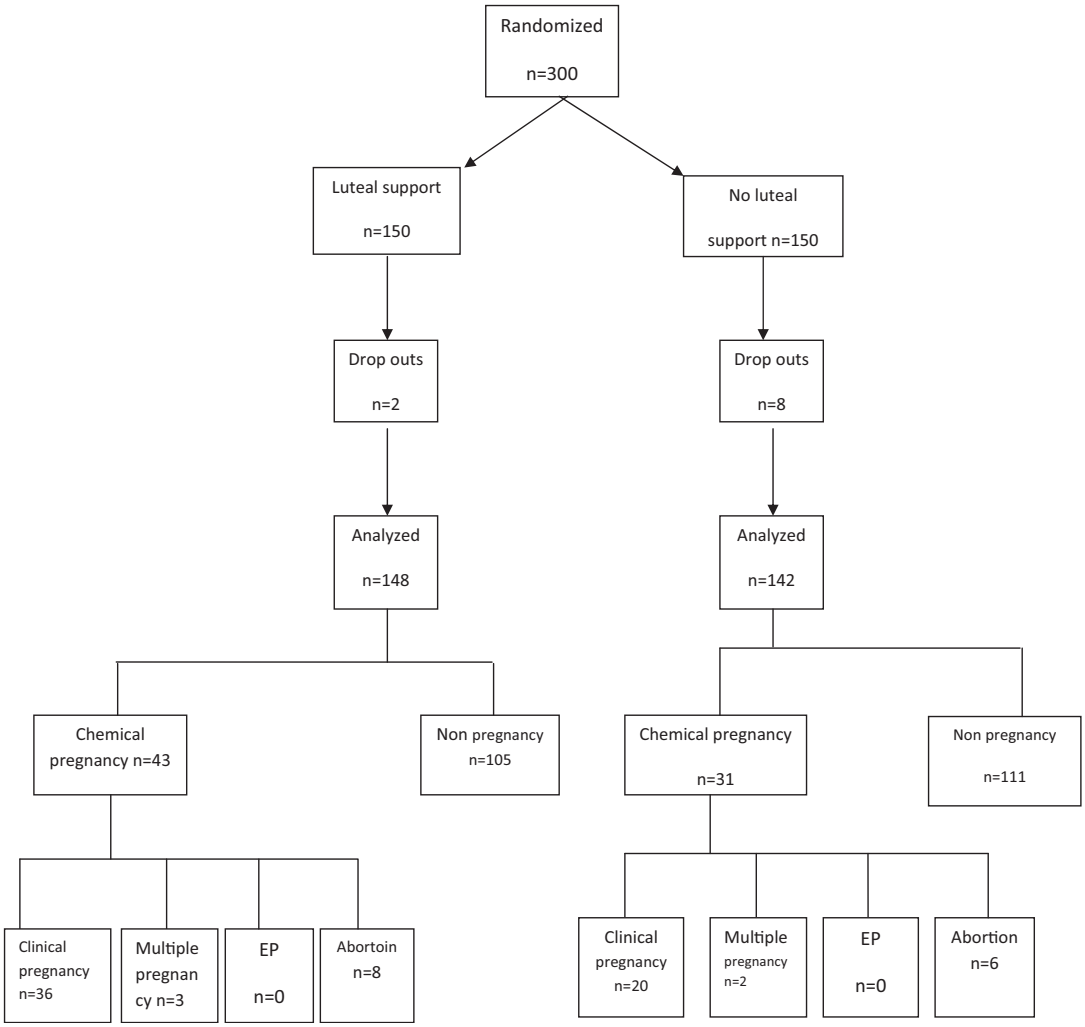

Fig. 1. Consort statement flow diagram through trial of luteal phase support versus no support for ovarian stimulation in intrauterine insemination cycles.

IUI cycles in the fertility outpatient clinic of our center and a private practice setting. All couples gave informed written consent before entering the study. All included women were between 18 and 35 years old, with a body mass index (BMI) of 18–28 kg/m^2, regular menses, no polycystic ovarian disease according to the Rotterdam criteria, basal FSH $<$ 10 IU/L, normal serum prolactin levels and normal thyroid function. All the couples had unsuccessfully been trying to conceive for at least one year before being enrolled in this trial. All women had bilateral tubal patency and a normal uterine cavity, confirmed by hysterosalpinography (HSG). Semen analyses were performed twice in men before treatment. Normal semen analyses were defined by the threshold values of World Health Organization (WHO) [11].

Women with diminished ovarian reserve, presence of a resistant ovarian cyst ($>$20 mm for $>$1 months), hypogonadotrophic hypogonadism and any contraindications to progesterone therapy were excluded from the study. All patients underwent transvaginal ultrasonography on day 2 or 3 of the menstrual cycle to assess normal ovarian reserve and their hormonal evaluations including LH, FSH, and estradiol were assessed. On the same day, patients initiated different stimulation of ovulation regimens. One group received clomiphene citrate (Cc) 50 mg tablets (Iran Hormone, Tehran, Iran) orally twice daily for 5 days, starting on day 3 of the menstrual cycle (38 patients, 38 cycles), and the other group received 5 mg of letrozole (Femara, Novartis Pharma Services, Basel, Switzerland) daily for 5 days, starting on day 3 of menses (94 patients). Some patients started Cc twice daily for 5 days, and then one hMG ampoule 75 IU (hMG, Meogon, Ferring Pharmaceuticals, and Malmo, Sweden) for 5 days was added starting on day 8 of the cycle (66 patients, 66 cycles). The other patients received 5 mg of letrozole daily for 5 days, starting on day 3 of the menses and a daily hMG ampoule 75 IU/IM for 5 days (87 patients, 87 cycles). HMG injection was started on day 8 of the menstrual cycle (the day after discontinuation of letrozole or Cc). Follicular diameter and endometrial thickness were measured by transvaginal ultrasound on the 12th day of the menstrual cycle and then every 2 days until the follicle reached 18 mm. When at least one follicle measuring 18 mm was observed, 10,000 IU of hCG (Pregnyl; N.V. Organon, Oss, The Netherlands) was injected.

After at least three days of sexual abstinence, semen samples were collected. Liquefaction of semen was performed at room temperature, and then the concentration, motility and morphology were evaluated according to the WHO criteria [11]. Afterwards, removal of seminal plasma was performed to avoid uterine contractions due to prostaglandins. The most available methods for removal of seminal plasma were centrifuging spermatozoa followed by re-suspension in adequate culture media [12].

The IUI was done by inserting 0.2–0.5 ml prepared sperm suspension into the uterus with a catheter (Soft-Pass J-SPI-068015; IN, USA) 36 h after hCG injection. The women rested in a supine position for 10 min after the IUI procedure.