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Oral dydrogesterone versus vaginal progesterone gel in the luteal phase support: randomized controlled trial

Vlatka Tomic [a,b,*], Jozo Tomic [a], Djurdja Zigmundovac Klaic [b], Miro Kasum [C], Krunoslav Kuna [a]

[a] Department of Gynecology and Obstetrics, University Clinical Centre "Sisters of Mercy", Zagreb, Croatia
[b] Department of Gynecology and Obstetrics, DZ Zagreb Centar, Zagreb, Croatia
[C] Department of Gynecology and Obstetrics, University Clinical Centre "Zagreb", Zagreb, Croatia

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ABSTRACT

Objectives: To compare efficacy, satisfaction and tolerability of oral dydrogesterone and micronized vaginal progesterone gel used for luteal supplementation.

Study design: Randomized controlled trial. A total of 853 infertile women undergoing IVF/ICSI treatment in University Hospital Center "Sisters of Mercy", Zagreb, Croatia.

Luteal support was provided as Crinone 8%® vaginal progesterone gel (90 mg) administered daily, or oral dydrogesterone Duphaston® (2× 10 mg) administered two times daily. Progesterone was administered from the day of oocyte retrieval (day 0) till pregnancy test or in a case of pregnancy, until week 10.

Results: The on-going pregnancy rates were comparable between Crinone 8%® vaginal progesterone gel and oral dydrogesterone – Duphaston® (28.1% versus 30.3%; OR 1.11 (0.82–1.49 with 95% CI)). Overall satisfaction and tolerability were significantly higher in the dydrogesterone group than in the Crinone group. Vaginal bleeding, interference with coitus and local adverse side effects such as vaginal irritation and discharge occurred significantly more in Crinone group than in dydrogesterone group.

Conclusions: Oral dydrogesterone is effective drug, well tolerated and accepted among patients and can be considered for routine luteal support.

Clinical trial registration number: NCT01178931; www.clinicaltrials.gov.

Introduction

The use of gonadotropin-releasing hormone (GnRH) agonists in the ovarian stimulation, which prevents a premature surge of luteal hormone (LH), ultimately leads to suppression of the pituitary gland [1]. Higher levels of estrogen observed during induced cycles result in inhibiting effect on the implantation of human embryos and though to underlie the corpus luteum dysfunction associated with IVF cycles [2]. The luteal support in in vitro-fertilization (IVF) cycles can be prolonged using human chorionic gonadotropin (hCG) and/or progesterone.

Since it has been noted that the use of hCG was related with higher risks of the onset of ovarian hyperstimulation syndrome (OHSS), progesterone is nowadays a product of choice in luteal support [3,4].

Currently vaginal progesterone is widely used, since the classic oral progesterone results in low bioavailability and lower pregnancy rate [5] and the intramuscular progesterone (IM-P) daily injections are painful and may cause abscesses, inflammatory reactions and local soreness [6,7]. Polyzos et al. [8] found that no significant difference exists between vaginal gel and all other vaginal progesterone forms in terms of clinical pregnancy rates, but Crinone 8% gel seems to be better accepted and preferred by patients [9,10].

However, standard protocol for luteal phase support has not been established (i.e. optimal dosage, route or duration).

Dydrogesterone is a synthetic retroprogesterone with good oral bioavailability [11]. Oral administration is very convenient for the

* Corresponding author at: DZ Zagreb Centar, Department of Gynecology and Obstetrics, Runjaninova 4, 10 000 Zagreb, Croatia. Fax: +385 1 37 68 272.
E-mail address: tomic.vlatka@gmail.com (V. Tomic).

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patients and may be even better tolerated than commonly used vaginal or IM-P. There are limited reports on the use of dydrogesterone in IVF cycles as luteal support [12–16]. The aim of this randomized controlled trial was to compare efficacy, tolerability and satisfaction rate of oral dydrogesterone and vaginal progesterone gel in the luteal phase support.

Materials and methods

The prospective, randomized, double-blinded clinical trial was conducted from October 2010 to October 2013 in a tertiary infertility unit at University Hospital Center "Sisters of Mercy", Zagreb, Croatia.

Patients were randomly assigned at the day of oocyte retrieval following computerized random number generator in procedure, to study or control group. Random allocation concealment with intervention drug was ensured by sequentially numbered, sealed, opaque envelopes. Patients were aware of the allocated arm since the treatment drugs have different route of administration, but investigators and outcome assessor were kept blinded to the allocation.

Eligible participants were all women undergoing controlled ovarian stimulation for IVF/ICSI treatment who met the following inclusion criteria: aged 18–45 years, a body mass index (BMI) $< 35\ kg/m^2$, applied routine short ovulation induction protocol with GnRH agonist, with less than three prior IVF cycles and at least one aspirated oocyte.

Exclusion criteria included: a history of dysfunctional uterine bleeding, recurrent miscarriage (defined as three or more spontaneous miscarriage), acute urogenital disease, transfer of frozen embryos and previous allergic reactions to progesterone products.

After screening and successful enrollment in the study, the participants underwent standard short ovarian hyperstimulation protocol with GnRH agonists. Gonadotropin releasing hormone (GnRH) analog was introduced with Triptorelin (Decapeptyl®, Ferring, Kiel, Germany) in form of subcutaneous injections, 2× 0.1 mg per day. From the 2nd day of ongoing cycle the recombinant FSH (rFSH, Gonal-F®, Serono, Bari, Italy or Puregon®, Organon Ltd., Dublin, Ireland) was subjoined according to individually adopted dosage, usually 225 IU and reduced to 150 IU in step-down regiment until a day of hCG application. The ovarian response was measured by serum level of estradiol (E2) and ultrasound monitoring. Gonadotropin stimulation was stopped when at least two follicles reached 17 mm in diameter. To trigger the final follicular maturation hCG (Brevactid®, Ferring, Kiel, Germany) 10000 IU was administered. Approximately 36–38 h later the aspiration of oocytes was performed under supervision of transvaginal ultrasound. Oocytes were afterwards cultivated in medium and 3–4 h later associated with sperm. Upon successful fertilization, the two best available embryos were selected and on the 2–5 day transferred into uterine cavity.

Patients were randomly assigned into one of the two groups – study group and the control group. Study group was receiving 2× 10 mg of oral dydrogesterone (Duphaston®, Abbot Biologicals B.V., Olst, Netherlands) from the day of oocyte retrieval until a pregnancy test or in the case of pregnancy until week 10. Control group was receiving 1× 90 mg of vaginal progesterone gel (Crinone 8%, Fleet Laboratories Ltd., Watford, UK) in the same fashion i.e. from the day of oocyte retrieval until pregnancy test or in the case of pregnancy until week 10.

Pregnancy was detected by 10 mIU/L serum level of β-hCG, approximately 2 weeks after ET and confirmed by the presence of gestational sac(s) at 6 weeks' gestation by transvaginal ultrasound. Spontaneous abortion is defined as the loss of clinical pregnancy before completed 22 weeks' gestation. An ongoing pregnancy is defined by the identification of fetal heartbeats at 12 weeks' gestation.

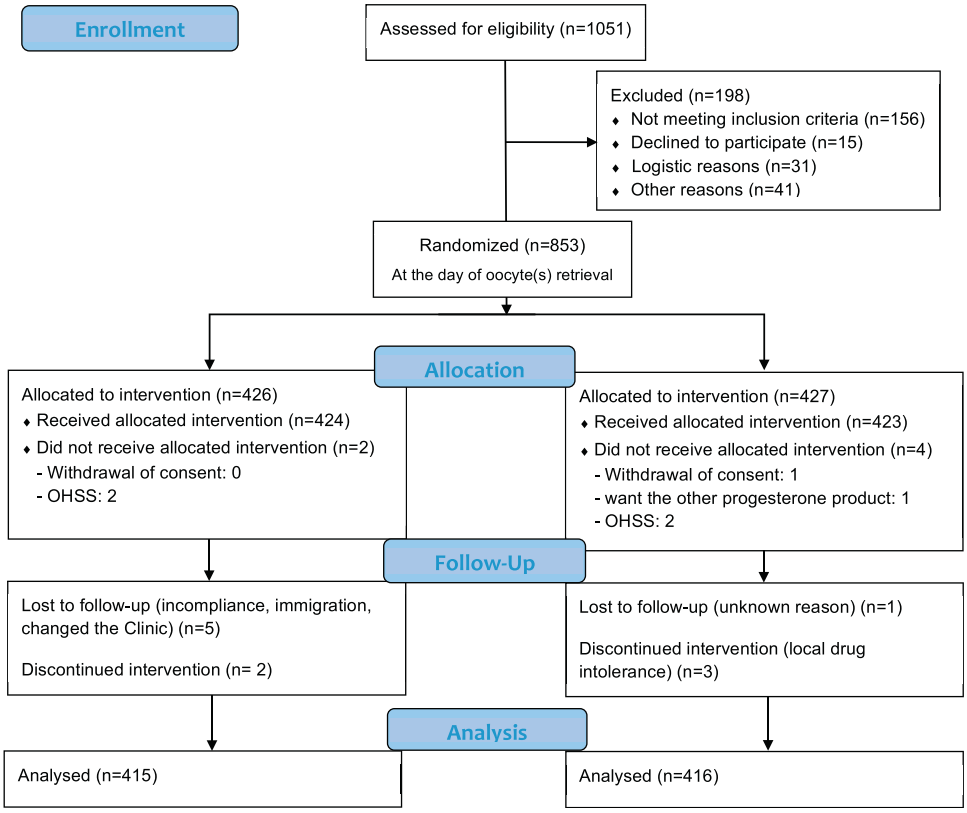

Fig. 1. Participant CONSORT flow diagram.