ORIGINAL ARTICLE: INFERTILITY

Impact of luteal phase support with vaginal progesterone on the clinical pregnancy rate in intrauterine insemination cycles stimulated with gonadotropins: a randomized multicenter study

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Objective: To evaluate the effect of luteal phase support (LPS) in intrauterine insemination (IUI) cycles stimulated with gonadotropins.
Design: Randomized multicenter trial.
Setting: Academic tertiary care centers and affiliated secondary care centers.
Patient(s): Three hundred and ninety-three normo-ovulatory patients, <43 years, with body mass index ≤30 kg/m^2, in their first IUI cycle, with at least one patent tube, a normal uterine cavity, and a male partner with total motile sperm count ≥5 million after capacitation.
Intervention(s): Gonadotropin stimulation, IUI, randomization to LPS using vaginal progesterone gel (n = 202) or no LPS (n = 191).
Main Outcome Measure(s): Clinical pregnancy rate, live-birth rate, miscarriage rate, and duration of the luteal phase.
Result(s): The primary outcome, the clinical pregnancy rate, was not statistically different between the treatment group (16.8%) and the control group (11%) (relative risk [RR] 1.54; 95% confidence interval [CI], 0.89–2.67). Similarly, the secondary outcome, the live-birth rate, was 14.9% in the treatment group and 9.4% in the control group (RR 1.60; 95% CI, 0.89–2.87). The mean duration of the luteal phase was about 2 days longer in the treatment group (16.6 ± 2.2 days) compared with the control group (14.6 ± 2.5 days) (mean difference 2.07; 90% CI, 1.58–2.56).
Conclusion(s): Although a trend toward a higher clinical pregnancy rate as well as live-birth rate was observed in the treatment group, the difference with the control group was not statistically significant.
Clinical Trial Registration Number: NCT01826747. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Duration luteal phase, intrauterine insemination, gonadotropin, luteal phase, MAR, randomized, progesterone, pregnancy rate

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Intrauterine insemination (IUI) is generally perceived as an infertility therapy with relatively low cost, low burden, and easy access. Gonadotropin stimulation combined with IUI has been proven to be effective for several indications including unexplained infertility, mild male infertility, and minimal–mild endometriosis (1–4).

The luteal phase is defined as the period between ovulation and the end of the menstrual cycle, marked by the onset of menses or establishment of a pregnancy (5). Normal luteal function requires optimal preovulatory follicular development, proper luteinization of the granulosa cells to produce progesterone, continued tonic luteinizing hormone (LH) support, vascularization of the corpus luteum, and estrogen to induce progesterone receptors in the endometrium (5). Ovarian stimulation with gonadotropins in the context of assisted reproductive technology (ART) is associated with luteal phase deficiency, which can be compensated by hormonal luteal phase support (LPS) (6). During a fresh ART cycle, deficiency in LPS is caused by the combination of hormone stimulation with gonadotropins, pituitary inhibition of LH and follicle-stimulating hormone (FSH) secretion with gonadotropin-releasing hormone (GnRH) agonists or antagonists, and follicular granulosa cell aspiration during egg retrieval, possibly impairing progesterone secretion from the corpus luteum. In contrast, hormone stimulation during an IUI cycle is typically performed with a lower dose of gonadotropins, without pituitary inhibition of LH or FSH secretion, and without follicular granulosa cell aspiration. The question thus remains as to whether mild ovarian stimulation with gonadotropins before IUI influences corpus luteum function and thus whether LPS is needed in these cycles.

The most common method of LPS in ART is vaginal administration of progesterone because of its neutrality regarding risk for ovarian hyperstimulation syndrome (7) and its ease of administration when compared with intramuscular injections of progesterone. So far, it is not clear whether LPS with vaginal progesterone is useful for treating possible luteal phase deficiencies after ovarian stimulation with gonadotropins in an IUI cycle. There has been insufficient clinical evidence that this approach is associated with an increased clinical pregnancy rate or live-birth rate compared with no LPS. In a randomized study (8), LPS with vaginal progesterone after ovarian stimulation and IUI increased the pregnancy rate from 12.7% to 21.1% per cycle and the live-birth rate from 9.3% to 17.4% per cycle. However, that study could be criticized for its high spontaneous conception rate between treatment cycles of 30%, the absence of power calculation, and the absence of concealment of allocation (8).

In our randomized, multicenter study, we tested the hypothesis that LPS with a vaginal progesterone gel after hormone stimulation with low-dose gonadotropins is associated with a higher clinical pregnancy rate (primary outcome variable) when compared with a control group who received no LPS. In addition, we documented the live-birth rate, miscarriage rate, and duration of luteal phase (number of days) as relevant secondary outcome variables.

MATERIALS AND METHODS

Patients

Between April 2011 and January 2015 we conducted an open-label, multicenter, randomized clinical trial (RCT) in nine participating sites in Belgium. The study protocol and informed consent form were approved by the institutional review board of the coordinating center (Leuven University Hospitals) (ML7232). This RCT was registered at ClinicalTrials.gov (NCT01826747) and as EudraCT number 2010-023867-17 (trial registration date: November 10, 2010; date of first patient's enrollment: April 2011).

All couples with an indication for IUI such as unexplained infertility, mild male factor infertility, or minimal–mild endometriosis were eligible for this study during their first IUI cycle. Before their inclusion in the study, all couples underwent a complete infertility evaluation, including a medical history, physical examination, serum hormone assays between days 2 and 5 of the menstrual cycle, pelvic ultrasound, assessment of tubal patency either by hysterosalpingography or laparoscopy, and semen analysis. Only normo-ovulatory patients <43 years old, with a body mass index ≤ 30, with at least one patent tube on hysterosalpingography and/or laparoscopy, with a normal uterine cavity, and with a partner whose sperm analysis showed a total motile sperm count of ≥ 5 million after capacitation were included.

Study Design

Eligible patients started gonadotropin stimulation only after informed consent had been obtained. Patients were randomized either before or during the stimulation period but before IUI was performed to receive either progesterone 8% vaginally or no LPS. Patients were randomized per block of 10 patients and per center through an Internet-based randomization system designed by the information technology department at Leuven University Hospital and managed by the Leuven University Fertility Center. Researchers were blinded to group allocations. Before the start of the study, the participating centers each received a center-specific login and password that granted access to the randomization Web site.

For days 2 to 3 of the menstrual cycle, the patients were prescribed 37.5–75.0 IU recombinant FSH (Gonal-F; Merck KGaA) to prevent multifollicular development of >2 follicles. In the absence of follicular growth (absence of follicles >10 mm) after 5 to 7 days, the dosage of the gonadotropins was increased by 37 IU.

Monitoring of the cycle was according to site-specific customs, with ultrasound and/or hormone analysis. Ovulation was triggered with recombinant human chorionic gonadotropin (rhCG, Ovitrelle; Merck KGaA) when a maximum of two dominant follicles was present. The IUI procedure was planned for between 32 and 40 hours after hCG administration or $\pm$24–26 hours after detection of a spontaneous LH surge. Both ultrasound and analysis of estradiol, LH, FSH, and progesterone were performed on the day of planning of the IUI (day of hCG administration or day of LH surge). Cycle cancellation or ovarian follicle aspiration followed by IUI was