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; 95% 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;106:1490–5. ©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

advised when ≥3 dominant follicles of ≥15 mm were detected to prevent high-order multiple pregnancies (9, 10).

Sperm preparation was performed according to local validated procedures. The patients were advised to rest in the supine position during 15 minutes immediately after IUI according to evidence from the literature (11).

In the control group, no LPS was provided. In the study group, LPS was provided with progesterone 8% vaginal gel (Crinone; Merck KGaA) once daily in the morning starting on the day after IUI until the time of pregnancy test (β-hCG) about 15 days after IUI. Crinone was administered by an applicator that delivered 1.125 g of vaginal gel containing 90 mg of progesterone. Clinical pregnancy was defined as the presence of an intrauterine or extrauterine fetus with positive heartbeat, on ultrasound at 6 to 8 weeks of amenorrhea (12). Live birth was defined as the live birth of a child beyond 24 weeks of gestation. Multiple live birth was defined as the birth of two or more infants.

Follow-up observation of the pregnancies and deliveries was performed in the hospitals from the participating centers and in other hospitals where the patients were referred for their obstetric care. Although there was no specific study protocol for follow-up observation of the pregnancies in our study, the clinical and obstetric data were systematically reported in a standardized way according to the requirements of the Belgian Register for Assisted Procreation (BELRAP), in line with the compulsory registration of IUI cycles in Belgium (13, 14).

Clinical Outcome Parameters

The primary outcome was clinical pregnancy rate per randomized cycle (positive ultrasound with gestational sac and at least one fetal heartbeat detected by ultrasound at ±7–8 weeks of amenorrhea). The secondary outcomes included live-birth rate, miscarriage rate, and duration of luteal phase between the day of hCG administration or LH peak and the first day of the next menstrual cycle in the absence of pregnancy. In a subanalysis, we compared the clinical pregnancy and live-birth rates in cycles with monofollicular and multifollicular responses, respectively.

Statistical Methods

Sample size calculation. Our objective was to test the hypothesis that when compared with no LPS, LPS with a vaginal progesterone gel leads to a higher clinical pregnancy rate (primary outcome) in a program of IUI after controlled ovarian stimulation with gonadotropins. We based our power calculation on a randomized study (8) in patients treated with IUI after ovarian stimulation with gonadotropins that obtained a clinical pregnancy rate of 21% in the study group with LPS with vaginal progesterone and 13% in the control group without LPS, resulting in a delta of 8%. In our study, assuming a delta of 10% at a power of 80%, with double-sided alpha at 5%, we calculated a sample size of 502 patients at the initiation of the study. Due to disappointing accrual, the study was stopped after 4 years of recruitment, with a total 393 patients included.

Statistical considerations. After randomization, an intention-to-treat analysis was performed for all cycles from all participating centers. The summary statistics are presented as mean and standard deviation (SD) for continuous variables, and as frequencies and percentages for categorical variables. Fisher exact and independent *t* test were used to compare the categorical and continuous variables, respectively, between the control cycles and LPS-treated cycles. Treatment effects on binary outcomes were analyzed using Poisson models with log link and are presented as relative risk (RR) with 95% confidence interval (CI). Treatment effects on continuous outcomes were analyzed using linear models and are presented as mean differences with 95% CI. Random intercepts were modeled in all outcome analyses to account for clustering by center. One-sided *P* values were reported for all outcome analyses. A 5% statistical significance level was assumed for all tests. A complete-case analysis was performed for the duration of the luteal phase, excluding patient records with pregnancy and records with missing observations. All analyses were performed using SAS software (version 9.4 for Windows; SAS Institute).

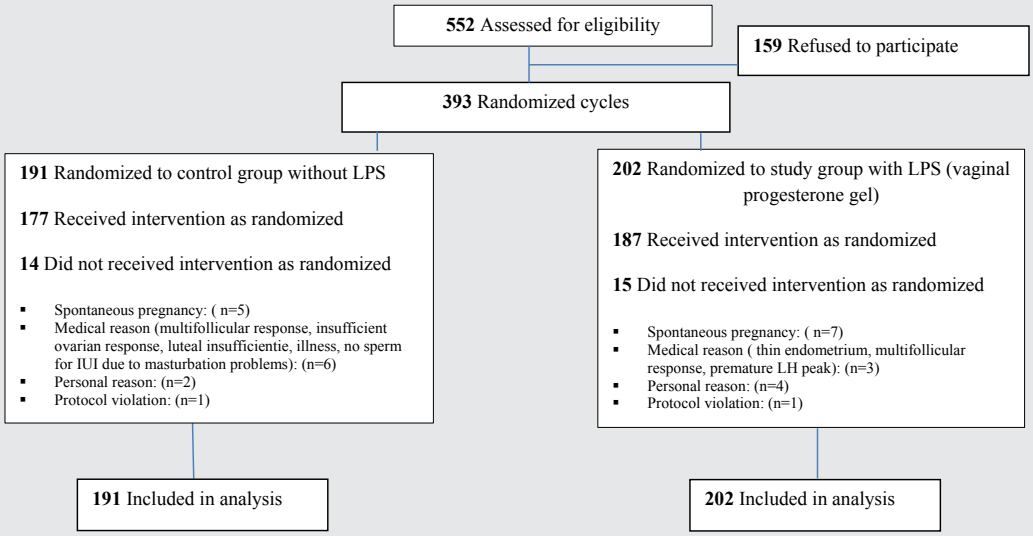
RESULTS

Between April 2011 and January 2015, 393 couples were randomized to the study group with LPS (n = 202) or the control group (n = 191) (Fig. 1). Both groups were comparable with respect to baseline clinical characteristics (Table 1) and IUI cycle parameters (gonadotropin dose, number of dominant follicles, number of cycles with selective follicular aspiration before IUI, sperm quality, endometrial thickness, and serum estradiol level at time of hCG injection) (Table 2). The proportion of women (in total 12 of 393 or 3% of all randomized cycles) who conceived spontaneously before the start of therapy was similar in both groups (see Fig. 1).

The clinical pregnancy and live-birth rates did not show a statistically significant difference between the treatment group (16.8% and 14.9%, respectively) and the control group (11% and 9.4%, respectively) [RR 1.54; 95% CI, 0.89–2.67; *P*=.12, and RR 1.60; 95% CI, 0.89–2.87; *P*=.12, respectively]. With an absolute risk difference of 6% (95% CI, −0.05 to 0.18) for pregnancy rate and 5% (95% CI, −0.05 to 0.16) for live-birth rate, the number of patients needed to treat was 17 to have one extra pregnancy, and 20 to achieve an extra live birth. The miscarriage rates were similar in both treatment (11.8%) and control (14.3%) groups (RR 0.8; 95% CI, 0.18–3.8; *P*=.80). The mean duration of the luteal phase was about 2 days (mean difference 2.1 days; 95% CI, 1.58–2.56; *P*<.0001) longer in the treatment group (16.6 ± 2.2 days, n = 137 cycles) compared with the control group (14.6 ± 2.5 days; n = 133 cycles) (Table 3).

A subanalysis was performed according to the response to ovarian stimulation to detect whether differences between the study and control groups were related to the response to ovarian stimulation. Both the cycles with monofollicular response (135 of 177; 76.3%) and multifollicular response (>1 follicle ≥14 mm at the time of hCG injection) had comparable results. In cycles with a monofollicular response,

FIGURE 1



Consolidated Standards of Reporting Trials (CONSORT) diagram of screening, randomization, and follow-up observation of study participants.

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the clinical pregnancy rate was 14.01% and the live-birth rate was 12.10% in the treatment group; this was comparable with 8.15% and 6.67%, respectively, in the control group (RR 1.75; 95% CI, 0.84–3.62; $P=.133$, and RR 1.85; 95% CI, 0.83–4.11; $P=.130$). In cycles with multifollicular response, the clinical pregnancy rate was 16.67% and live-birth rate was 13.33% in the treatment group; this was comparable with 14.29% and 11.90%, respectively, in the control group (RR 1.09; 95% CI, 0.32–3.75; $P=.892$, and RR 1.11; 95% CI, 0.29–4.27; $P=.881$). There were two dichorial diamniotic twins in the study group (2 of 30; 7%) and none in the control group (0 of 18).

TABLE 1

Baseline clinical characteristics per patient in intrauterine insemination study with and without luteal phase support.

Variable	Control group (n = 191)[a]	Study group (n = 202)[a]
Female age (y), mean ± SD	31.5 ± 3.8	31.0 ± 3.97
BMI (kg/m^2), mean ± SD	23.0 ± 3.2	23.2 ± 3.4
Cycle duration (d), mean ± SD	28.9 ± 2.4	28.9 ± 2.2
Infertility type, n (%)		
Primary	120 (63)	143 (71)
Secondary	70 (37)	58 (29)
Infertility duration (mo), mean ± SD		
Primary	28.6 ± 20.0	26.5 ± 19.7
Secondary	27.0 ± 18.4	26.8 ± 16.3
Treatment indication, n (%)		
Anovulation	3 (2)	7 (4)
Endometriosis	16 (8)	20 (10)
Male factor	66 (35)	77 (38)
Mixed	43 (23)	38 (19)
Tubal factor	7 (4)	3 (2)
Unexplained	55 (29)	56 (28)

Note: BMI = body mass index; SD = standard deviation.
[a] One missing value.

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DISCUSSION

In this multicenter RCT, we did not confirm the hypothesis that LPS with a vaginal progesterone gel after hormone stimulation with low-dose gonadotropins is associated with a statistically significant higher clinical pregnancy rate (fetal heart rate positive) when compared with no administration of LPS. The results should be interpreted recognizing that the study ended up being underpowered to demonstrate $P<.05$, and thus is not adequate to answer the research question. However, because of the large size of the study, these data can be used in future meta-analyses on this topic and are therefore relevant. Miscarriage and live births were also not affected. However, there was an absolute risk difference for the clinical pregnancy rate of 6% and live-birth rate of 5% in the study group with LPS. The duration of the luteal phase was statistically significantly longer (about 2 days) in the study group with LPS than in the control group without LPS.

Our study is marked by several strengths. First, to the best of our knowledge, it includes the highest number of patients ever included in an RCT allowing only one cycle per patient to test this hypothesis. Second, the randomization method was objective and allowed stratification per center (computer-generated random allocation). Third, the data were analyzed using an intention-to-treat approach. Fourth, the duration of the luteal phase was investigated for the first time in an RCT. Our observation that the duration of the luteal phase was 2 days longer in women receiving LPS with progesterone is novel but not surprising in view of the physiologic action of progesterone on the estrogen-primed endometrium. In view of the growing awareness of patient-centeredness in fertility treatment and decision making (15), it is important to inform the patient about this prolonged luteal phase, which may be a burden in patients who are waiting for the outcome of the treatment. Our

TABLE 2

Intrauterine insemination cycle characteristics in study with and without luteal phase support.

Variable	Control group (177 cycles)	Study group (187 cycles)	*P* value
Total motile sperm count after capacitation, mean (95% CI) (million)	28.2 (23.3; 33.2)	28.2 (23.4; 33.1)	.998
Endometrial thickness (mm) at the time of hCG injection, mean (95% CI)	8.4 (8.2; 8.7)	8.6 (8.3; 8.8)	.418
No. of dominant ovarian follicles with a diameter ≥14 mm at the time of hCG injection, mean (95% CI)	1.2 (1.2; 1.3)	1.2 (1.1; 1.2)	.119
Sperm origin, percentage of cycles using donor sperm (%)	8/177 (4.5)[a]	9/187 (4.8)[a]	≥.999
Selective ovarian follicular aspiration before IUI (%)	5/177 (2.8)[a]	2/187 (1.1)[a]	.272
Serum 17β-estradiol level (pg/mL) at day of hCG administration, mean (95% CI)	311 (288; 334)	289 (266; 311)	.173
Total dose of gonadotropins, mean (95% CI)	381 (351; 411)	390 (361; 419)	.679
Monofollicular response, n/N (%)	135/177 (76.27)	157/187 (83.96)	.086
Multifollicular response, n/N (%)[b]	42/177 (23.73)	30/187 (16.04)	

Note: Unless otherwise indicated, data were analyzed using an independent *t* test. All reported *P* values are two-sided. CI = confidence interval; IUI = intrauterine insemination; hCG = human chorionic gonadotropin.
[a] Analyzed using Fisher's exact test.
[b] More than one follicle ≥14 mm.

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hypothesis that most patients will accept this inconvenience because luteal support is associated with a statistically significant higher clinical pregnancy rate requires further investigation.

Our study is also marked by several limitations. First, the open-label design and the absence of a placebo control group represent possible sources of treatment bias. Second, the results are derived from a smaller sample size than initially intended (78% of the initial sample size calculation); thus, the study ended up being underpowered to demonstrate $P<.05$, but the results are in line with similar studies that showed a higher clinical pregnancy rate in the LPS group although they were not statistically significant (8, 16, 17).

The results of our study support other evidence from a systematic review that showed improved reproductive outcomes after LPS with progesterone in women treated with a combination of gonadotropins and IUI (18). In a subanalysis of this systematic review, the clinical pregnancy rate after IUI improved after LPS with progesterone after ovarian stimulation with gonadotropins (odds ratio [OR] 1.77; 95% CI, 1.2–2.6). We would like to point out that the RR 1.54 for clinical pregnancy with LPS in our study is similar to the OR 1.77 for clinical pregnancy found in this meta-analysis. However, it cannot be concluded that LPS with progesterone can improve clinical pregnancy rates in any woman who receives ovarian stimulation before IUI because no difference was found after ovarian stimulation with clomiphene citrate (CC) (OR 0.89; 95% CI, 0.47–1.67) or with a combination of CC and gonadotropins (OR 1.34; 95% CI, 0.81–2.23). According to Hill et al. (18), this subanalysis suggests that endogenous corpus luteum function may be decreased in gonadotropin cycles and be normal or supported in CC cycles. However, it is important to note that reproductive outcome after IUI cycles is reported to be significantly better after ovarian stimulation with gonadotropins than after ovarian stimulation with CC, even in the absence of LPS (4, 19).

It has been hypothesized that LPS after IUI is especially beneficial after ovarian stimulation with gonadotropins resulting in multifollicular response, based on the assumption that multifollicular response is associated with higher early luteal phase estradiol levels secreted by multiple corpora

TABLE 3

Reproductive outcome per randomized cycle (intention-to-treat analysis) and per intrauterine insemination cycle (per-protocol analysis).

Variable	Control group	Study group	Relative risk (95% CI)	Absolute risk differences % (95% CI)	*P* value
Per randomized cycle	191 cycles	202 cycles			
FHB + pregnancy rate	21/191 (11%)	34/202 (16.8%)	1.54 (0.89; 2.67)	0.06 (−0.05; 0.18)	.12[a]
LBR per cycle	18/191 (9.4%)	30/202 (14.9%)	1.60 (0.89; 2.87)	0.05 (−0.05; 0.16)	.12[a]
Miscarriage rate	3/21 (14.3%)	4/34 (11.8%)	0.8 (0.18; 3.8)	−0.03 (−0.22; 0.17)	.80[a]
	133 cycles	137 cycles	Mean differences		
Mean duration luteal phase (d): (±SD) (95% CI)	14.6 ± 2.5	16.6 ± 2.2	2.07 (1.58; 2.56)		<.0001[b]
Per IUI cycle	177 cycles	187 cycles	Relative risk		
FHB + pregnancy rate	17/177 (9.6%)	27/187 (14.4%)	1.52 (0.82; 2.79)	0.05 (−0.04; 0.15)	.18[a]
LBR per cycle	14/177 (7.9%)	23/187 (12.3%)	1.57 (0.81; 3.07)	0.04 (−0.04; 0.13)	.18[a]
Miscarriage rate	3/17 (17.7%)	4/27 (14.8%)	0.84 (0.18; 3.892)	−0.03 (−0.28; 0.22)	.82[a]

Note: CI = confidence interval; FHB = fetal heartbeat; IUI = intrauterine insemination; LBR = live-birth rate; SD = standard deviation.
[a] Binary outcomes: relative risk with 95% CI + *P* value (two-sided test; Poisson model with log-link).
[b] Continuous outcome: mean differences with 95% CI + *P* value (two-sided test).

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lutea, inhibiting via negative feedback pituitary LH secretion required for optimal corpus luteum function (8, 17). Although this hypothesis was not addressed in our study, which used a relatively low starting rFSH dose, it was not supported by our subanalysis showing a similar trend to improved reproductive outcome after either monofollicular or multifollicular response.

It is not clear whether the data from our study can be extrapolated to other forms of luteal support after IUI, as there is no consensus on the dose or type for luteal support in IUI cycles (16, 18, 20). In our study, patients from the study group applied a vaginal gel containing 8% of progesterone, once a day, with a total dose of 90 mg per application. A recent RCT (21) that demonstrated that clinical pregnancy rate was not improved after LPS with 200 mg of vaginal progesterone when compared with no LPS can be criticized for its lack of power calculation, lack of intention-to-treat analysis, high drop-out rates (10.6%), and patients potentially being randomized several times without apparent control for the presence of multiple measures in the statistical analysis. In a dose-finding study (20), the ongoing clinical pregnancy rate was similar after vaginal LPS with 300 mg or 600 mg of progesterone after ovarian stimulation with gonadotropins and IUI, but that study lacked a power calculation as well. All randomized trials on this issue lack power calculation, and it is also not clear whether the hypothesis was tested two sided.

CONCLUSIONS

In conclusion, our multicenter study, the largest RCT testing the hypothesis on the patient level, demonstrated that in patients treated with IUI after ovarian stimulation with gonadotropins, the clinical pregnancy rate was not statistically significantly higher after LPS with a vaginal progesterone gel (17%) than in patients without LPS (11%). However, these data are derived from a sample size smaller than intended with the initial power calculation. The large sample size of our study and the similar findings of the meta-analysis suggest there may be a benefit of supplementing the luteal phase in patients with an indication for IUI stimulated with gonadotropins, independent of a monofollicular or multifollicular response.

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