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ARTICLE

Luteal phase support with progesterone does not improve pregnancy rates in patients undergoing ovarian stimulation with letrozole

BIOGRAPHY

Elizabeth Dilday is a board-certified obstetrician and gynecologist who is completing her final year of Reproductive Endocrinology and Infertility fellowship at the David Geffen School of Medicine at UCLA. She previously completed her residency training at Parkland Memorial Hospital/UT Southwestern Medical Center, where she served as administrative chief resident.

Elizabeth Dilday[1,*], Marisa Gigg[1], Luis Hoyos[1,2], Molly Quinn[3], Daniela Markovic[4], Lindsay Kroener[1]

KEY MESSAGE

This analysis of 492 letrozole ovarian stimulation cycles assessed effects of exogenous vaginal progesterone for luteal phase support. Exogenous progesterone did not improve clinical pregnancy rates in this analysis. These results have clinical significance because many providers empirically prescribe luteal support, which comes with additional patient cost, inconvenience and discomfort.

ABSTRACT

Research question: Does luteal phase support with vaginal progesterone improve clinical pregnancy rates in patients undergoing ovarian stimulation with letrozole?

Design: This was a retrospective cohort study of patients undergoing ovarian stimulation with letrozole paired with intrauterine insemination (IUI) or timed intercourse (TIC) from January 2018 to October 2021. The primary outcome of clinical pregnancy rate (CPR) was calculated for cycles with and without luteal phase progesterone support. Univariate logistic regressions were done to evaluate predictor variables for CPR. Clinically important covariates including age, body mass index, anti-Müllerian hormone concentration, diagnosis of ovulatory dysfunction and multifollicular development were included in a multivariate analysis evaluating the relationship between luteal progesterone use and odds of clinical pregnancy. Secondary outcomes including spontaneous abortion, biochemical pregnancy and ectopic pregnancy were calculated. Live birth rates were calculated for cycles in a secondary analysis.

Results: A total of 492 letrozole ovarian stimulation cycles in 273 patients were included. Of these cycles, 387 (78.7%) used vaginal progesterone for luteal support and 105 (21.3%) did not. The unadjusted CPR per cycle was 11.6% (45/387) with progesterone and 13.3% (14/105) without progesterone ($P = 0.645$). After adjusting for significant covariates including age, BMI, diagnosis of ovulatory dysfunction and multifollicular development, the odds for clinical pregnancy were not significantly improved in cycles with exogenous progesterone (odds ratio [OR] 1.15, 95% confidence interval [CI] 0.48–2.75, $P = 0.762$). A follow-up analysis demonstrated that live birth rate was 10.7% (41/384) with and 12.5% (13/104) without luteal progesterone, respectively ($P = 0.599$).

Conclusions: Luteal support with vaginal progesterone does not significantly improve CPR in ovarian stimulation cycles using letrozole.

[1] UCLA Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, David Geffen School of Medicine, Los Angeles CA, USA
[2] IVF Florida Reproductive Associates, Miami FL, USA
[3] Department of OB/GYN and Reproductive Endocrinology and Infertility, Keck School of Medicine at University of Southern California, Los Angeles CA, USA
[4] UCLA Department of Internal Medicine, David Geffen School of Medicine, Los Angeles CA, USA

*Corresponding author. E-mail address: Elizabeth.dilday@gmail.com (E. Dilday). https://doi.org/10.1016/j.rbmo.2022.09.012
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Vaginal progesterone

INTRODUCTION

In the luteal phase of the menstrual cycle, progesterone produced by the corpus luteum prepares the endometrium for successful implantation and subsequent maintenance of pregnancy (*van der Linden et al., 2015*). Synchrony between the endometrium and embryo is dependent on appropriate timing and degree of progesterone exposure. In natural ovulation, following the mid-cycle LH surge, pulsatile release of LH from the pituitary is essential for corpus luteum support in early pregnancy. Between 7 and 9 weeks of gestation, the placenta takes over progesterone production during the 'luteo-placental shift' (*Csapo, 1969*).

There is a biological rationale to explain how fertility treatments may interfere with normal luteal phase progesterone production and therefore necessitate exogenous supplementation. During IVF, supraphysiologic oestradiol concentrations associated with ovarian stimulation may down-regulate pituitary LH secretion that is essential to support progesterone release from the corpus luteum (*de los Santos et al., 2012*). Use of gonadotrophin-releasing hormone (GnRH) antagonists or agonists may also negatively impact LH secretion. Additionally, during fresh transfers that follow IVF, mechanical follicular disruption from oocyte retrieval may directly disrupt corpus luteum function. Numerous studies have demonstrated improved pregnancy and live birth rates (LBR) with the use of progesterone following treatment with assisted reproductive technologies (ART) and this is now routine practice (*Green et al., 2017*).

While the benefits of luteal progesterone in IVF are clear, its utility in ovarian stimulation cycles is less clear. When paired with intrauterine insemination (IUI) or timed intercourse (TIC), ovarian stimulation does not involve aspiration of follicular fluid, and the endogenous production of progesterone following ovarian stimulation with human chorionic gonadotrophin (HCG) trigger may provide sufficient luteal support (*Green et al., 2017*). Additionally, oestradiol concentrations are not elevated to the same degree in ovarian stimulation cycles as they are in IVF cycles, and therefore there is probably less pituitary suppression. Studies have found improved pregnancy rates only in those ovarian stimulation cycles using gonadotrophins, but not in cycles using clomiphene citrate (Clomid®) (*Green et al., 2017*). These results are supported by a systematic review and meta-analysis that evaluated exogenous progesterone luteal support after ovulation induction/IUI cycles that included 11 randomized controlled trials (*Green et al., 2017*).

Despite the limited data to support routine use, luteal progesterone is widely used in non-IVF fertility treatments. A web-based survey examined use of empiric luteal phase progesterone in non-IVF treatments and found that 73.5% of obstetrician-gynaecologists (OBGYN) and 100% of reproductive endocrinology and infertility specialists (REI) surveyed prescribed progesterone for luteal phase support (*Weedin et al., 2020*). While 56% of REI physicians considered treatment type to guide prescribing progesterone, still close to half routinely gave luteal progesterone regardless of treatment type. This study demonstrates the lack of uniformity and widespread use of luteal progesterone. Furthermore, data looking at the role of luteal progesterone specifically in ovarian stimulation cycles using letrozole (Femara®) is extremely limited. Only one randomized controlled trial examined the effects of progesterone in letrozole/IUI cycles. This study included multiple ovarian stimulation medications with a letrozole arm of 96 patients (56 with luteal support, 40 without luteal support). No significant differences in clinical pregnancy rates were demonstrated across all subgroups, but a direct comparison of letrozole with and without luteal phase progesterone was not performed (*Agha-Hosseini et al., 2012*). Additionally, LBR was not examined in this study. In light of the heterogeneous use of luteal phase progesterone across all treatments and limited data available on its use with letrozole, the goal of the present study was to determine whether luteal phase progesterone in letrozole ovarian stimulation cycles leads to improved CPR.

MATERIALS AND METHODS

The Institutional Review Board (IRB) at the University of California, Los Angeles, approved the retrospective study protocol and analysis (IRB#20-000795, approved 26 June 2020). All letrozole ovarian stimulation cycles paired with IUI or TIC from 1 January 2018 to 31 October 2021 at an academic fertility centre were screened for inclusion. Cycles were excluded for cancellation, total motile sperm count less than 5 million at the time of IUI, or use of any additional stimulation medications including clomiphene citrate or gonadotrophins in conjunction or simultaneously.

Ovulation stimulation protocol

Baseline transvaginal ultrasound was performed on cycle day 2 or 3 and letrozole 2.5, 5 or 7.5 mg was initiated daily for 5 days. Patients were followed with serial ultrasounds until at least one dominant follicle was noted. In cases where no follicular growth was seen, patients were re-dosed with higher doses of letrozole in a step-wise fashion. Subcutaneous HCG (Ovidrel® 250 µg, EMD Serono, Inc. Rockland, MA, USA or Novarel® 10,000 units, Ferring Pharmaceutical, Parsippany, NJ, USA) was administered when lead follicle diameter reached approximately 20 mm. When IUI was performed, patients returned approximately 36 h after trigger injection. Male partners were instructed to abstain from ejaculation for 24–36 h prior to sperm collection. Donor sperm samples were thawed per protocol. A single IUI using a Cook catheter was performed under transabdominal ultrasound guidance. Patients undergoing TIC were given instructions on timing and frequency of intercourse relative to HCG trigger (TIC nightly for three consecutive nights starting on night of trigger).

When given, vaginal micronized progesterone (Prometrium®) 200 mg (Virtus Pharmaceuticals, Inc., Langhorne, PA, USA) twice daily or three times daily was initiated 2 days after IUI or 4 days post-HCG trigger in TIC. Progesterone supplementation was empiric and serum progesterone concentrations were not monitored in the luteal phases of cycles. The decision to use progesterone, as well as dosing and frequency, was provider-dependent. Home urine pregnancy test was done 14 days after IUI or TIC and positive pregnancy tests were confirmed with serial serum HCG testing. Patients returned to clinic for their first obstetric ultrasound to assess pregnancy location and appropriate gestational development at approximately 6 weeks of gestation and continued weekly ultrasounds until transfer to obstetric care at approximately 8–10 weeks of gestation.

Study variables and statistical analysis

Baseline patient demographic characteristics were recorded for each patient including age, body mass index (BMI), gravidity, parity, infertility diagnosis, ethnicity and anti-Müllerian hormone (AMH), when available. Patients were grouped into two diagnosis categories, those with ovulatory dysfunction including polycystic ovary syndrome (PCOS), and all other diagnoses including but not limited to unexplained infertility, diminished ovarian reserve, male factor infertility and use of donor spermatozoa. Patients were divided into two groups based on AMH concentration, those with an AMH concentration <1.5 ng/ml and all others with AMH concentration ≥1.5 ng/ml.

Cycles were classified based on presence or absence of luteal progesterone support. Other cycle features assessed were letrozole dose and number of dominant follicles at the time of HCG trigger. If letrozole was re-dosed, cycles were classified by the final dose prescribed. Dominant follicles were defined as ≥14 mm in average diameter and cycles were classified as having either unifollicular or multifollicular development.

The primary outcome was clinical pregnancy rate (CPR), defined as visualization of a fetal pole with cardiac motion on obstetric ultrasound. Secondary outcomes included miscarriage (defined as spontaneous abortion or missed abortion at <20 weeks of gestation), biochemical pregnancy and ectopic pregnancy. A follow-up analysis was done to compare LBR per cycle (defined as delivery of one or more live infants at ≥20 weeks of gestation), gestational age at delivery and birthweight between the two groups for all cycles. The primary outcome data were available for all subjects. The follow-up analysis was only performed for subjects who had data available and were not lost to follow-up.

Categorical variables were compared across groups based on progesterone status using the logistic model. Continuous variables were compared across the groups using the linear regression model. For each model, SE was adjusted to account for non-independence of multiple cycles from the same patient, as appropriate. All analyses were performed using the cycle as the unit of analysis, while *P*-values were adjusted as appropriate to account for clustered observations. Specifically, the general estimating equation (GEE) logistic model was used to assess the relationship between progesterone use and odds of clinical pregnancy, taking into account that observations (cycles) within the same patient were not independent.

Statistical analysis used exact chi-squared, logistic regression or linear regression with adjustments for clustering, and GEE logistic models, where appropriate. Univariate logistic regressions were done to evaluate possible predictor variables for CPR. Significant covariates including age, BMI, IUI versus TIC, diagnosis of ovulatory dysfunction and multifollicular development were included in a multivariate analysis evaluating the relationship between progesterone use and odds of clinical pregnancy. The relationship between progesterone status and odds of clinical pregnancy was evaluated before and after adjusting for pre-specified covariates using the GEE logistic model. The associations between progesterone status and secondary outcomes among patients who had a positive pregnancy test were evaluated using the exact chi-squared test. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

An *a priori* sample size calculation was not performed as this was a sample of convivence that included all cycles over a 4-year span. However, a post hoc power analysis was performed. Based on the current sample size of 492 cycles, it was possible to confirm a difference in CPR of 11% between progesterone treated versus non-treated groups with 80% power at the usual significance level of 0.05. The above difference in proportions corresponds to an odds ratio of 2.1 in the progesterone treated versus non-treated groups. The above analysis assumed that about 80% of cycles were treated with progesterone and that the CPR in the non-treated group was 13%.

RESULTS

A total of 492 letrozole ovarian stimulation cycles in 273 patients were included. Of the included cycles, 387 (78.7%) used vaginal progesterone for luteal support and 105 (21.3%) did not. The groups were comparable with respect to age, BMI, AMH concentration, infertility diagnosis of ovulatory dysfunction and nulliparity. In the group of patients who received progesterone, 40.8% had a diagnosis of ovulatory dysfunction/PCOS and 59.2% had another infertility diagnosis. In the group of patients who did not receive progesterone, 54.3% had a diagnosis of ovulatory dysfunction/PCOS and 45.71% another infertility diagnosis ($P = 0.079$). Patients receiving progesterone were significantly more likely to undergo IUI, with IUI performed in 81.7% of cycles with progesterone versus 61.9% of cycles without progesterone ($P = 0.0017$). There was no difference in multifollicular development between those patients who did and did not receive progesterone ($P = 0.337$) (TABLE 1).

There was no difference in unadjusted CPR in cycles with and without progesterone (11.6% vs 13.3%, $P = 0.645$). Of the cycles with positive pregnancy tests, there were no differences in miscarriage ($P = 0.581$) or biochemical pregnancy rates ($P = 0.314$) (TABLE 2). Only one ectopic pregnancy occurred in a patient who had received progesterone. After adjusting for significant covariates including age ($P = 0.038$), BMI ($P = 0.0045$), diagnosis of ovulatory dysfunction ($P = 0.0285$) and multifollicular development ($P = 0.0695$), the odds of clinical pregnancy were not significantly improved in cycles using luteal progesterone (odds ratio [OR] 1.15, 95% confidence interval [CI] 0.48–2.75, $P = 0.762$). There was no difference in unadjusted CPR in IUI versus TIC cycles (11.3% vs 14.4%, $P = 0.401$), so this was not included in the adjustment for significant covariates.

In the follow-up analysis, the live birth rate was similar between the two groups. In the progesterone group, LBR was 10.7% (41/384) and was 12.5% (13/104) in the group that did not utilize luteal progesterone ($P = 0.599$). Three patients in the progesterone group and one patient in the no progesterone group with clinical pregnancies were lost to follow-up after transfer of care and were excluded from the LBR analysis. The mean gestational age at delivery was 272 days in the progesterone group and 266 days in the no progesterone group ($P = 0.055$). While this difference in gestational age approached statistical significance, it was not clinically significant. Furthermore, the infant weight at delivery was similar between the two groups (3159 g vs 2896 g, $P = 0.076$).

TABLE 1 DEMOGRAPHICS AND CYCLE CHARACTERISTICS OF PATIENTS WHO DID AND DID NOT RECEIVE PROGESTERONE

Characteristic	Patients who received progesterone (*n* = 387)	Patients who did not receive progesterone (*n* = 105)	*P*-value
Age (years)	35.1 ± 3.7	34.0 ± 3.8	0.225
BMI (kg/m^2)	25.7 ± 6.8	24.9 ± 6.2	0.988
AMH concentration >1.5 ng/ml	76.2	86.7	0.089
Nulliparity	82.7	75.2	0.237
Multifollicular development	51.2	45.7	0.337
IUI cycles	81.7	61.9	0.0017
Diagnosis of ovulatory dysfunction	40.8	54.3	0.079

Data are presented as mean ± SD or %.

AMH = anti-Müllerian hormone; BMI = body mass index; IUI = intrauterine insemination.

DISCUSSION

This retrospective analysis of 492 letrozole cycles at a single academic fertility centre found that use of exogenous progesterone for luteal phase support was not associated with improved odds of clinical pregnancy after adjustment for significant covariates. These results have the potential to impact clinical care because many providers empirically prescribe luteal phase support for ovarian stimulation/IUI cycles (*Weedin et al., 2020*). Vaginal progesterone supplementation comes with additional cost, inconvenience and discomfort for patients during fertility treatment. Each cycle requires a minimum of 12 days of treatment and additionally up to 8 weeks' gestation in patients who do achieve pregnancy, and many patients undergo multiple cycles before achieving success (*Cohlen et al., 2018*).

A few small studies have investigated the role of luteal progesterone in letrozole cycles focusing specifically on PCOS patients. One retrospective review evaluated the effect of luteal phase progesterone on CPR in PCOS women treated with clomiphene citrate (Ralingtonpharma LLP, India) (n = 90) or letrozole (n = 31). In this study, letrozole (Tocris Bioscience, Minneapolis, MN, USA) was used as second-line treatment in patients initially treated with clomiphene citrate if they had no response, if the endometrial lining was thin, or if 3–6 clomiphene citrate cycles were unsuccessful, making the letrozole group poorer prognosis. Out of 51 letrozole cycles in 31 patients, CPR were 21.1% (8/38) in the progesterone group compared with 0% (0/13) in the non-progesterone group (*Montville et al., 2010*). After excluding TIC cycles and analysing exclusively IUI cycles, pregnancy rates were 20.8% (5/24) with progesterone and 0% (0/8) without progesterone ($P < 0.01$). While a benefit to luteal progesterone was shown, the number of cycles was small and pregnancy rates did not correspond to those in previously published studies. The authors suggest that the benefit shown in this population may be the result of progesterone down-regulation of endometrial androgen receptors, which have elevated expression in women with PCOS (*Montville et al., 2010*). Another prospective study investigated 186 clomiphene citrate-resistant PCOS patients to assess whether luteal phase support with vaginal dydrogesterone (Duphaston®, Maitri Pharmaceuticals, India) following ovulation induction improves CPR (Rezk *et al.*, 2018). Over three cycles, patients who received luteal vaginal dydrogesterone had a significantly higher CPR than patients who received letrozole alone (48.9% versus 23.9%, $P < 0.001$). Possible explanations for the observed effects in PCOS patients include an abnormal hypothalamic response to progesterone that can be circumvented with exogenous progesterone, in addition to activation of the inherent ability of granulosa cells to secrete normal concentrations of progesterone when ovulation occurs (*Rezk et al., 2019*).

These studies differ from the current study as they included solely PCOS patients, many of whom used letrozole as a second-line agent after failure of one or more treatment cycles. The use of letrozole has recently been expanded to patients who do not carry a diagnosis

TABLE 2 CLINICAL OUTCOMES OF PATIENTS WHO DID AND DID NOT RECEIVE PROGESTERONE

Outcome	Cycles with progesterone (*n* = 387)	Cycles without progesterone (*n* = 105)	*P*-value
Clinical pregnancy rate, unadjusted (%)	11.6	13.3	0.645
Clinical pregnancy rate, adjusted odds ratio[a]	1.15 (0.48–2.75)	1.00	0.762
Miscarriage[b] (per positive pregnancy test)	5/55 (9.1)	0/16 (0.0)	0.581
Ectopic (per positive pregnancy test)	1/55 (1.8)	0/16 (0.0)	0.999
Biochemical pregnancy (per positive pregnancy test)	3/55 (5.5)	2/16 (12.5)	0.314
Live birth rate, unadjusted	41/384 (10.7)	13/104 (12.5)	0.599

Data are presented as n (%) unless otherwise stated.

[a] Odds ratio adjusted for age, BMI, AMH, diagnosis of ovulatory dysfunction, multifollicular development.

[b] Miscarriage defined as missed abortion or spontaneous abortion.

of PCOS. While use of letrozole was initially shown to result in higher live birth and ovulation rates in a subset of PCOS women compared to the use of clomiphene (*Legro et al., 2014*), it now has a role in other patients. The use of letrozole compared with clomiphene had statistically non-inferior conception, pregnancy and live birth rates in the setting of unexplained infertility and may be used as a first-line agent in these patients as well as in those who have had a thin endometrial lining with clomiphene citrate treatment (*Diamond et al., 2015*). Observational studies have also proposed a lower multiple pregnancy rate with letrozole (*Diamond et al., 2015*).

Strengths of the current study include the inclusion of a patient population using letrozole for a variety of indications, as well as patients who underwent both IUI and TIC. This is a practical reflection of the populations served and treatments offered at most fertility clinics and makes these results more generalizable than the findings from previous studies. The sample size is larger than prior studies and did look at LBR as an outcome.

Study limitations include the observational, non-randomized study design. The relatively small proportion of patients who did not receive luteal progesterone is an additional limitation. Furthermore, while the study did control for the diagnosis of ovulatory dysfunction, the broad inclusion of patients with all infertility diagnoses may fail to identify specific sub-populations who may benefit from luteal progesterone. Finally, all patients in the study received a subcutaneous HCG trigger injection. It is possible that this could offer some luteal phase support, as HCG prompts the corpus luteum to produce progesterone continuously via mimicking LH pulsatility, although notably this was consistent across both study groups (*Beckers et al., 2000*; *Belaisch-Allart et al., 1990*; *Dashti and Eftekhar, 2021*; *Kupferminc et al., 1990*). Historically, it was felt that HCG should be the primary choice for luteal phase support (*Dashti and Eftekhar, 2021*). While HCG does initially provide luteal support, the mean half-life of exogenous HCG after injection is 2.3 days and its effects are limited to the 10 days after ovulation (*Damewood et al., 1989*). Given the limited duration of HCG effect and its minimal effect in supporting a pregnancy post-implantation, there is benefit to progesterone supplementation over HCG for luteal phase support. An analysis of the effect of the HCG trigger on luteal phase support was outside the scope of this retrospective study.

The LBR data that were collected in a follow-up analysis were overall reassuring, with similar LBR with and without luteal progesterone use. While gestational age and birthweight at delivery trended higher with luteal progesterone use, neither reached statistical significance. More importantly, the mean gestational ages were all at term, and the differences observed were not clinically significant. While this cohort of patients with live birth was small and a few patients were lost to follow-up, this data overall do not demonstrate significant difference between the groups. In summary, this retrospective study of patients with all infertility diagnoses receiving letrozole for ovarian stimulation demonstrates that luteal phase support with progesterone did not improve CPR. A larger, randomized prospective study with more delineation of diagnosis and indication for letrozole is needed to further validate these findings.

In conclusion, Luteal phase support with exogenous vaginal progesterone, which comes with additional cost and discomfort for patients, did not significantly improve CPR in ovarian stimulation cycles using letrozole in this study. Eliminating progesterone in these cycles could improve the patient experience by simplifying treatment without compromising outcomes. Larger prospective randomized studies are needed to validate these results.

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