



Luteal phase support in intrauterine insemination cycles

İntrauterin inseminasyon sikluslarında luteal faz desteği

İsmet Gün¹, Özkan Özdamar², Ali Yılmaz¹

¹Gülhane Military Medical Academy, Haydarpaşa Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey

²İstanbul Medeniyet University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Intrauterine insemination (IUI) treatment aims to increase the rate of conception by increasing the chances that the maximum number of healthy sperm reach the site of fertilization. IUI with controlled ovarian stimulation is frequently used in assisted reproduction practice. Although widely used, the efficacy of luteal support in IUI remains controversial. In this article, we aimed to review what we know regarding luteal support in IUI cycles and to adjudicate about the clinical use and benefits of this treatment. Based on the study results available in the literature, it appears to be beneficial to supplement the luteal phase in gonadotropin-stimulated IUI cycles that yield more than one follicle.

Keywords: Intrauterine insemination, controlled ovarian stimulation, luteal phase support

Öz

İntrauterin inseminasyon (İUİ) tedavisi, maksimum sayıda sağlıklı spermin fertilizasyon bölgesine ulaşma şansını artırarak gebelik oranını artırmayı hedefler. Kontrollü ovaryan stimülasyon ile İUİ, yardımıyla üreme pratiği sıklıkla kullanılmaktadır. Yaygın kullanımına rağmen, İUİ'de luteal desteğin etkinliği halen tartışmalıdır. Bu makalede, İUİ sikluslarında luteal destek hakkında bildiklerimizi gözden geçirmeyi ve bu tedavinin klinik kullanımı ve faydaları hakkında hükme varmayı hedefledik. Literatürdeki çalışma sonuçlarına göre, birden fazla follikül elde edilen gonadotropinle indüklenmiş İUİ sikluslarında luteal fazing desteklenmesi faydalı gibi görünmektedir.

Anahtar Kelimeler: İntrauterin inseminasyon, kontrollü ovaryan stimülasyon, luteal faz desteği

PRECIS: Based on the study results in the literature, it appears to be beneficial to supplement the luteal phase in gonadotropin-stimulated intrauterine insemination cycles that yield more than one follicle.

Introduction

The aim, frequency, and success rate of intrauterine insemination

Intrauterine insemination (IUI) is an artificial insemination technique in which sperm is introduced directly into the uterine cavity irrespective of whether ovulation has been triggered. The purpose of this process is to increase the rate of conception by improving the sperm quality and concentration and by transporting the maximum number of healthy sperm to the site of fertilization. Controlled ovarian stimulation (COS), which involves a variety of ovulation induction (OI) agents, is used before the procedure in an effort to increase the number of oocytes, eliminate ovulation disorders that are not detected during regular examinations, and provide the optimal conditions for insemination.

Although the cost-effectiveness of IUI has been questioned, it is a widely-used fertility treatment that gives patients a good chance of pregnancy with relatively lower cost as compared with in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI); however, the difference between the two is significant. Within the context of the European IVF Monitoring Programme in 2004, data from 19 countries were analyzed. It was reported that IUI was performed in 98.388 of a total of 245.099 cycles, or 40.1% of infertile patients, (52.866 IVF cycles and 93.845 ICSI cycles), and 12.081 births (12% per cycle) were reported in these IUI cycles, with a multiple pregnancy rate of 13%. The same data indicated that the number of donor inseminations was relatively high (with a 2004 donor insemination cycle number of 17.592, a pregnancy rate per cycle of 17.7%, and a multiple pregnancy rate of 11.8%)⁽¹⁾. The European Society of Human

Reproduction and Embryology (ESHRE) also reported that IUI practices in Europe have increased over the years, and 162.843 IUI cycles with 29.235 donor cycles for IUI were carried out in 2009⁽²⁾. This outcome is not surprising given that IUI is employed in a broad range of indications including mild male infertility, unexplained infertility, and minimal or mild endometriosis. The effectiveness of IUI depends on a set of variables including the extent of IUI use, the indications for IUI, the optimal procedures for sperm preparation, insemination methods and timing, and the need to prevent premature luteinizing hormone (LH) surges and luteal deficiency in stimulated IUI cycles⁽³⁾.

The main problem with IUI cycles with respect to the data in question is that pregnancy rates per cycle are lower as compared with IVF/ICSI, for which there are many possible reasons. The leading one may be that the amount of research focused on IUI is not sufficient. A literature search on PubMed using the phrase IUI revealed that the first publication on this issue was published by in 1962 and also yielded 2.233 publications since October 2015. In contrast, when PubMed is searched using the phrase IVF, the resulting number of hits is 38.340. There are nearly 17 times as many IVF studies as there are IUI studies. Consequently, these data indicate that although frequently employed, IUI is not adequately studied. For this reason, we suppose that there are many unknowns to be analyzed. One of which is whether luteal phase support (LPS) is necessary for IUI cycles. When the current literature was investigated using the phrase LPS in IUI, PubMed yielded 42 publications since October 2015 on this subject. These publications include two meta-analyses in 2013 and very few controlled prospective studies to date. Moreover, the Cochrane database does not have any articles on the topic.

Known facts and observational study results

An LH surge is needed for follicle rupture and oocyte maturation. Similarly, progesterone (P) is needed to support early pregnancy and implantation. P is a product of the corpus luteum (CL) and provides secretory transformation of the endometrium during the luteal phase. In order for P receptors to diffuse sufficiently, a sufficient amount of estrogen (E) is needed⁽⁴⁾. In all COS cycles, multiple follicular development and the resultant supraphysiologic estradiol block the hypothalamic-pituitary axis with negative feedback, and hence the necessary LH oscillation for CL function does not occur. Consequently, this situation causes defective P and premature luteolysis⁽⁵⁾.

Analysis of the available observational studies revealed that the luteal phase in gonadotropin-stimulated cycles is 20% shorter (an average luteal phase lasts 11 days), and that this shortness can be normalized by administering mid-luteal human chorionic gonadotropin (hCG), and that groups receiving LPS had significantly higher levels of mid-luteal P than those receiving no support⁽⁶⁻⁹⁾. However, mid-luteal P levels were

<10 ng/mL in only one-third of the cycles that had a shortened luteal phase. This demonstrates that mid-luteal P levels are not directly related with luteal function⁽⁶⁾. Additionally, P plays a crucial role in LH secretion modulation, and long-term exposure to P or E+P can reduce LH secretion^(10,11).

Exogen hCG administration can reduce LH concentrations through short and long feedback mechanisms⁽¹²⁾. However, more comprehensive studies demonstrated that hCG injection does not induce down-regulation of LH secretion during the luteal phase in normoovulatory women in spite of multifollicular development in unstimulated cycles and therefore supraphysiologic steroid concentration⁽¹³⁾. On the other hand, ovarian stimulation and the related multifollicular development are associated with abnormal endometrium progression during the early luteal period in almost 50% of cases⁽¹⁴⁾.

Premature luteinizing hormone surge in intrauterine insemination cycles

An LH surge is triggered by the increasing levels of E secreted by the dominant follicle and is a requirement for follicular rupture and oocyte maturation. A premature LH surge is defined as a premature rise of LH (>10 IU/L) accompanied by a concomitant rise in P (>1 mg/L-3.2 nM/L)⁽¹⁵⁾. With the exception of natural cycles in older women, premature LH surge is a rarely-encountered phenomenon, although in stimulated IUI cycles its rate approaches 25-30%^(15,16). Premature LH surges may result in cycle cancellation or treatment failures. Gonadotropin-releasing hormone antagonists correct the premature LH surge but do not affect pregnancy rates, which indicates that it is not completely a case of early luteinization or premature LH surge⁽¹⁵⁾.

Meta-analysis and prospective randomized controlled studies for luteal phase support in intrauterine insemination cycles

Despite some controversies in the published literature, luteal deficit and its causes are clarified thanks to progress in assisted reproduction technique. From this perspective, the usefulness of P supplementation during the luteal phase in IVF/ICSI cycles for reproductive outcomes is notably accepted in the Cochrane study. However, the timing of initiation, duration, route and amount of administration are still debated⁽¹⁷⁾. On the other hand, the effects of LPS in IUI cycles are unclear. To date, a very limited number of randomized controlled prospective studies has been conducted regarding the necessity of LPS treatment in stimulated IUI cycles. IUI cycles resemble IVF cycles in terms of multifollicular production and represent supraphysiologic steroid production. In this regard, it could be plausible to consider that the number of follicles in stimulated IUI cycles does matter and that LPS may be needed in multifollicular cases. The relevant literature investigation with regard to stimulated IUI cycles + LPS produced only two studies that addressed the

issue of follicle number. The first is the report of ESHRE Capri Workshop Group in 2009, which assessed six randomized controlled studies including 456 patients⁽³⁾. In this report, it was stressed that LPS treatment was not a major requisite for mild gonadotropin-stimulation IUI cycles (1-2 follicles). The second was the study by Seckin et al.⁽¹⁸⁾ in 2014, which compared women who received a vaginal P gel with controls in an unexplained infertility population undergoing gonadotropin-stimulated IUI cycles. According to the results of this study, it was suggested that there were no difference between groups that received and did not receive LPS in terms of clinical pregnancy rates (CPR) and live birth rates (LBR) per cycle and per patient; however, in the IUI cycles that yielded a multifollicular response (>1 dominant follicle), LPS treatment statistically increased the CPR per patient compared with those with monofollicular response (28.2% vs. 11.4%, respectively, $p=0.04$). This result was the first evidence that LPS affected the success of the multifollicular result in gonadotropin-stimulated IUI cycles.

A literature search with regards to prospective randomized controlled trials (RCT) revealed the first study was conducted by Erdem et al.⁽¹⁹⁾ in 2009. In this study, groups receiving and not receiving vaginal P gel for LPS two days after IUI in rFSH-stimulated IUI cycles in patients with unexplained infertility were

compared. The results revealed that both CPR per cycle (21.1% and 12.7%, $p=0.028$, respectively) and per patient (39.4% and 23.8%, $p=0.01$, respectively) and LBR per cycle (17.4% and 9.3%, $p=0.016$, respectively), and per patient (35.8% and 18.1%, $p=0.003$, respectively) were significantly higher in the LPS-receiving group. Multiple pregnancy rates (MPR) did not significantly differ between the groups. This was the first prospective randomized controlled study to be conducted in this field that provided live birth rates. To date, there have been two meta-analyses,^(20,21) including five RCTs^(19,22-25) regarding this issue. Although all five RCTs included in the two meta-analyses provided biochemical pregnancy rate (BPR), CPR, MPR, and miscarriage rates (MR), the studies conducted by Erdem et al.⁽¹⁹⁾, Ebrahimi et al.⁽²³⁾, and Maher⁽²⁴⁾, also assessed LBR. None of the studies indicated a difference between MPR and MR. Vaginal P was used for LPS in all these studies. Meta-analyses by Hill et al.⁽²⁰⁾ and Miralpeix et al.⁽²¹⁾ revealed significantly higher CPRs [OR: 1.47; 95% CI: (1.15-1.98) and RR: 1.41; 95% CI: (1.14-1.76), respectively] and LBRs [OR: 2.11; 95% CI: (1.21-3.67) and RR: 1.94; 95% CI: (1.36-2.77), respectively] in LPS-administered groups as compared with LPS-free groups. In the subgroup analyses, LPS was reported to significantly increase BPR, CPR, and LBR only in the gonadotropin-stimulated IUI cycles compared with the LPS-free group. However, none of the

Table 1. Characteristics of the randomized controlled trials that assessed luteal phase support in women undergoing intrauterine insemination cycles

	Total no of patients	No of treatment / control cycles	Stimulation of ovulation	Luteal support, dosage, duration	Outcomes
Erdem et al. ⁽¹⁹⁾ , 2009	214	223/204	rFSH	Vaginal progesterone gel, 90 mg/24 h, once daily, until 12 th wk.	CPR, BPR, LBR, MPR, MR
Kyrou et al. ⁽²²⁾ , 2010	468	196/204	Clomiphene citrate	Vaginal progesterone suppositories, 200 mg/8 h, until 7 th wk.	CPR, BPR, MPR, MR
Ebrahimi et al. ⁽²³⁾ , 2010	200	252/259	Clomiphene citrate + hMG	Vaginal progesterone suppositories, 400 mg/24 h, once daily, until 10 th wk.	CPR, BPR, LBR, MPR, MR
Maher ⁽²⁴⁾ , 2011	71	132/126	rFSH	Vaginal progesterone gel, 90 mg/24 h, once daily, for 14 days.	CPR, BPR, LBR, MPR, MR
Agha-Hosseini et al. ⁽²⁵⁾ , 2012	300	148/142	Clomiphene citrate, Clomiphene citrate + hMG, Letrozole, Letrozole + hMG	Vaginal progesterone suppositories, 400 mg/24 h, once daily, until 12 th wk.	CPR, BPR, MPR, MR
Hossein Rashidi et al. ⁽²⁶⁾ , 2014	253	NA	Clomiphene citrate + hMG	Vaginal progesterone suppositories, 400 mg/12 h, twice Daily, until 8 th wk.	CPR, BPR, MR
Khosravi et al. ⁽²⁷⁾ , 2015*	150	NA	Clomiphene citrate + rFSH	Vaginal progesterone suppositories, 400 mg/24 h, once daily.	CPR, MR

rFSH: Recombinant follicular stimulating hormone, hMG: Human menopausal gonadotropin, CPR: Clinical pregnancy rate, BPR: Biochemical, pregnancy rate, LBR: Live birth rate, MPR: Multiple pregnancy rate, MR: Miscarriage rate, Wk: Week, NA: Not available, *Groups received oral dydrogesterone versus vaginal progesterone suppositories for luteal phase support.

Table 2. Reproductive outcomes of randomized controlled trials that assessed luteal phase support in women undergoing intrauterine insemination cycles

	BPR (%) (p)	CPR (%) (p)	LBR (%) (p)
Erdem et al. ⁽¹⁹⁾ , 2009	25.1%-13.7% (0.002)	21.2%-12.7% (0.028)	17.4%-9.3% (0.016)
Kyroue et al. ⁽²²⁾ , 2010	-	7.3%-8.7% (NS)	-
Ebrahimi et al. ⁽²³⁾ , 2010	13.5%-11.2% (NS)	11.5%-10% (NS)	7.5%-5.7% (NS)
Maher ⁽²⁴⁾ , 2011	37.1%-20.6% (0.004)	29.5%-19.8% (0.07)	18.9%-5.5% (<0.001)
Agha-Hosseini et al. ⁽²⁵⁾ , 2012	29%-21.8% (NS)	24.3%-14.1% (0.02)	-
Hossein Rashidi et al. ⁽²⁶⁾ , 2014	30.8%-22.2% (NS)	15.8%-12.7%, (NS)	-
Khosravi et al. ⁽²⁷⁾ , 2015*	-	25.7%-29.7% (NS)	-

Data are presented as percentage rates in groups receiving luteal phase support versus no support. BPR: Biochemical pregnancy rate, CPR: Clinical pregnancy rate, LBR: Live birth rate, NS: Not significant, *Groups received oral dydrogesterone versus

studies present data regarding the number of follicles yielded. In addition, Miralpeix et al.⁽²¹⁾ categorized the five studies assessed in their meta-analyses as either low risk of bias (if all the questions were answered yes) or high risk of bias (if at least one question was answered no) with respect to the responses to six parameters, which were "sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues." Consequently, studies conducted by Kyrou et al.⁽²²⁾ and Ebrahimi et al.⁽²³⁾ were defined as having a high risk of bias, whereas the others had a low risk of bias.

After the above-mentioned meta-analyses, two more double-blinded prospective randomized controlled studies were published, both of which were conducted in Iran. The first was a placebo-controlled study in 2014 by Hossein Rashidi et al.⁽²⁶⁾ which involved vaginal P for LPS administered until the 8th gestational week. COS was achieved with clomiphene citrate (100 mg/d) and human menopausal gonadotropin (75 IU/d) in the study groups. No statistically significant difference was detected between the groups receiving LPS (n=127) and placebo (n=126) in terms of BPR (30.8-22.2%, p=0.15, respectively), CPR (15.8-12.7%, p=0.30, respectively), MR (10-18.8%, p=0.45, respectively) and the ongoing pregnancy rate (OPR) (46.2-46.4%, p=0.98, respectively). The second study was conducted in 2015 by Khosravi et al.⁽²⁷⁾ in which vaginal P (400 mg) and oral dydrogesterone (20 mg) groups were compared for LPS with regards to CPR, MR, and mid-luteal P values (seven days after IUI). Although there was no statistical difference, the mid-luteal P level in the oral dydrogesterone arm was higher and, accordingly, MR was lower. Consequently, this study demonstrated that oral dydrogesterone could also be effective for LPS as vaginal P in COS+IUI cycles. The characteristics and reproductive outcomes of the RCTs available in the literature are demonstrated in detail in Tables 1 and 2.

Conclusion

In conclusion, COS+IUI cycles are similar to IVF/ICSI cycles in terms of multifollicular development. Only a limited number of randomized controlled trials are available about LPS in

IUI cycles. Based on the results of these studies, it appears to be beneficial to support the luteal phase in gonadotropin-stimulated IUI cycles that yield more than one follicle. There is still a need for further randomized controlled trials to evaluate the effectiveness of LPS treatment in stimulated IUI cycles.

Ethics

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: İsmet Gün, Özkan Özdamar, Design: İsmet Gün, Özkan Özdamar, Data Collection or Processing: İsmet Gün, Özkan Özdamar, Ali Yılmaz, Analysis or Interpretation: İsmet Gün, Özkan Özdamar, Ali Yılmaz, Literature Search: İsmet Gün, Özkan Özdamar, Ali Yılmaz, Writing: İsmet Gün, Özkan Özdamar.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, et al. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod* 2008;23:756-71.
- Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, et al. Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. *Hum Reprod* 2013;28:2318-31.
- ESHRE Capri Workshop Group. Intrauterine insemination. *Hum Reprod Update* 2009;15:265-77.
- Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. *Hum Reprod Update* 2007;13:581-90.
- Fausser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. *Trends Endocrinol Metab* 2003;14:236-42.
- Olson JL, Rebar RW, Schreiber JR, Vaitukaitis JL. Shortened luteal phase after ovulation induction with human menopausal gonadotropin and human chorionic gonadotropin. *Fertil Steril* 1983;39:284-91.

7. Grazi RV, Taney FH, Gagliardi CL, Von Hagen S, Weiss G, Schmidt CL. The luteal phase during gonadotropin therapy: effects of two human chorionic gonadotropin regimens. *Fertil Steril* 1991;55:1088-92.
8. Messinis IE, Bergh T, Wide L. The importance of human chorionic gonadotropin support of the corpus luteum during human gonadotropin therapy in women with anovulatory infertility. *Fertil Steril* 1988;50:31-5.
9. Blumenfeld Z, Nahhas F. Luteal dysfunction in ovulation induction: the role of repetitive human chorionic gonadotropin supplementation during with the luteal phase. *Fertil Steril* 1988;50:403-7.
10. Soules M, Steiner RA, Clifton DK, Cohen NL, Aksel S, Bremner WJ. Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. *J Clin Endocrinol Metab* 1984;58:378-82.
11. Nippoldt TB, Reame N, Kelch RP, Marshall JC. The roles of estradiol and progesterone in decreasing luteinizing hormone pulse frequency in the luteal phase of the menstrual cycle. *J Clin Endocrinol Metab* 1989;69: 67-76.
12. Tavaniotou A, Albano C, Smits J, Devroey P. Comparison of LH concentrations in the early and mid-luteal phase in IVF cycles after HMG alone or in association with GnRH antagonist Cetrorelix. *Hum Reprod* 2001;16:663-7.
13. Tavaniotou A, Devroey P. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. *Fertil Steril* 2003;80:654-5.
14. Garcia JE, Acosta AA, Hsiu JG, Jones HW Jr. Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin/human chorionic gonadotropin for in vitro fertilization. *Fertil Steril* 1984;41:31-5.
15. Lambalk CB, Leader A, Olivennes F, Fluker MR, Andersen AN, Ingerslev J, et al. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod* 2006;21:632-9.
16. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/ antagonists) for intrauterine insemination (IUI) in women with sub fertility. *Cochrane Database Syst Rev* 2007:CD005356.
17. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev* 2011;5:CD009154.
18. Seckin B, Turkcapar F, Yildiz Y, Senturk B, Yilmaz N, Gulerman C. Effect of luteal phase support with vaginal progesterone in intrauterine insemination cycles with regard to follicular response: a prospective randomized study. *J Reprod Med* 2014;59:260-6.
19. Erdem A, Erdem M, Atmaca S, Guler I. Impact of luteal phase support on pregnancy rates in intrauterine insemination cycles: a prospective randomized study. *Fertil Steril* 2009; 91:2508-13.
20. Hill MJ, Whitcomb BW, Lewis TD, Wu M, Terry N, DeCherney AH, et al. Progesterone luteal support after ovulation induction and intrauterine insemination: a systematic review and meta-analysis. *Fertil Steril* 2013;100:1373-80.
21. Miralpeix E, González-Comadran M, Solà I, Manau D, Carreras R, Checa MA. Efficacy of luteal phase support with vaginal progesterone in intrauterine insemination: a systematic review and meta-analysis. *J Assist Reprod Genet* 2014;31:89-100.
22. Kyrou D, Fatemi HM, Tournaye H, Devroey P. Luteal phase support in normo-ovulatory women stimulated with clomiphene citrate for intrauterine insemination: need or habit? *Hum Reprod* 2010;25:2501-6.
23. Ebrahimi M, Asbagh FA, Darvish S. The effect of luteal phase support on pregnancy rates of the stimulated intrauterine insemination cycles in couples with unexplained infertility. *Int J Fertil Steril* 2010;4:51-6.
24. Maher MA. Luteal phase support may improve pregnancy outcomes during intrauterine insemination cycles. *Eur J Obstet Gynecol Reprod Biol* 2011;157:57-62.
25. Agha-Hosseini M, Rahmani M, Alleyassin A, Safdarian L, Sarvi F. The effect of progesterone supplementation on pregnancy rates in controlled ovarian stimulation and intrauterine insemination cycles: a randomized prospective trial. *Eur J Obstet Gynecol Reprod Biol* 2012;165:249-53.
26. Hossein Rashidi B, Davari Tanha F, Rahmanpour H, Ghazizadeh M. Luteal phase support in the intrauterine insemination (IUI) cycles: a randomized double blind, placebo controlled study. *J Family Reprod Health* 2014;8:149-53.
27. Khosravi D, Taheripanah R, Taheripanah A, Tarighat Monfared V, Hosseini-Zijoud SM. Comparison of oral dydrogesterone with vaginal progesterone for luteal support in IUI cycles: a randomized clinical trial. *Iran J Reprod Med* 2015;13:433-8.