

## Review Article

# GnRH Agonist Addition to Routine Luteal Phase Support in Assisted Reproductive Technology

Yavuz Emre Şükür<sup>1</sup>, Coskun Şimşir<sup>2</sup>, Elif Didem Özdemir<sup>1</sup> and Murat Sönmezer<sup>1\*</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Ankara University School of Medicine, Turkey

<sup>2</sup>Department of Obstetrics and Gynecology, Liv Hospital, Turkey

\*Corresponding author: Murat Sönmezer, Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, A.D. 06100, Cebeci, Ankara, Turkey

Received: December 21, 2015; Accepted: January 29, 2016; Published: February 01, 2016

## Abstract

Luteal phase defect is a frequent problem in assisted reproductive technology cycles most probably as a result of supraphysiological steroid levels that inhibit corpus luteum functions. Luteal phase supports essential to counter luteal phase defect to ensure an optimal implantation, pregnancy and delivery rate. Today, the routine luteal phase support is established by progesterone administration. Recently, GnRH agonists have been evaluated to increase the success rates of routine luteal phase support. The possible mechanisms with GnRH agonists for luteal phase support include stimulation of corpus luteum by pituitary LH secretion, activation of local GnRH receptors on endometrium, and possibly effecting trophoblast cells. Recent data demonstrated that implantation rates may increase with adjunctive use of GnRH agonists. However definitive effect of GnRH agonists as an additional agent to support luteal phase should be clarified in large scale studies in both fresh agonistic and antagonistic GnRH analog cycles and frozen thawed cycles.

**Keywords:** Assisted reproductive technology; GnRH agonist; Luteal phase support; Progesterone

## Abbreviations

hCG: human Chorionic Gonadotropin; LPD: Luteal Phase Defect; ART: Assisted Reproductive Technology; GnRH: Gonadotropin Releasing Hormone; IVF: *In Vitro* Fertilization; LH: Luteinizing Hormone; LPS: Luteal Phase Support; RCT: Randomized Controlled Trial; OPU: Oocyte Pick-Up; ICSI-ET: Intracytoplasmic Sperm Injection And Embryo Transfer

## Introduction

The luteal phase is characterized by the formation of corpus luteum secreting progesterone, which is essential for progression of a pregnancy. Progesterone provides endometrial receptivity by secretory transformation of endometrium and prepares the endometrium for nidation and implantation of embryo [1]. It also promotes local vasodilatation and myometrial quiescence by inducing decidual nitric oxide synthesis [2]. Human Chorionic Gonadotrophin (hCG) secreted from the blastocysts maintains the persistence of corpus luteum during the early pregnancy period [3]. Approximately 8% of infertile patients suffer from Luteal Phase Defect (LPD) in their natural cycles [4].

Luteal phase defect is a frequent problem in Assisted Reproductive Technology (ART) cycles as a result of supraphysiological steroid levels, aspiration of granulosa cells during oocyte retrieval, and Gonadotropin Releasing Hormone (GnRH) agonist use. The aim of pituitary down-regulation with GnRH agonist in *In Vitro* Fertilization (IVF) treatment cycles is to reduce the cycle cancellation risk due to premature luteinization and premature LH surge [5]. The advantages of GnRH agonist use prior to gonadotropin stimulation are increased number of mature oocytes and improved pregnancy rates [6]. However, this method also results in LPD in almost all patients by inhibiting corpus luteum [7,8]. Administration of hCG for final

oocyte maturation in stimulated IVF cycles was another suggested cause for LPD. It was suggested that hCG suppresses Luteinizing Hormone (LH) production via a short-loop feedback mechanism [9]. However, this effect could not be proven in unstipulated cycles of normo-ovulatory women [10]. In GnRH antagonist cycle's luteolysis is also initiated prematurely and luteal phase was shortened and lower pregnancy rates were achieved [11]. Hence, Luteal Phase Support (LPS) is also necessary in GnRH antagonist IVF cycles.

Luteal phase support is considered essential to counter LPD and improves implantation, pregnancy and delivery rates [12-14]. The first LPS modalities include administering hCG and progesterone and both had similar effects on pregnancy rates [15]. However, with the use of hCG the risk of ovarian hyper stimulation syndrome increased and progesterone has become the primary agent for LPS in IVF cycles [16,17]. Although hCG supports the luteal phase indirectly by stimulating corpus luteum, progesterone induces secretory transformation of the endometrium in the luteal phase and improves endometrial receptivity [1]. Progesterone for LPS can be administered via oral, intramuscular, vaginal or rectal routes, but optimal route of progesterone has not yet been established [15]. Some other LPS modalities such as estrogens, steroids, ascorbic acid and acupuncture have been also identified in co-treatment protocols with progesterone but none of these were found to be effective [18-20].

Recently, GnRH agonists have been evaluated for LPS. Both subcutaneous and intranasal routes of GnRH agonists were used to support luteal phase in different studies [21-24]. One of the possible mechanisms for LPS with GnRH agonists is stimulatory effects on corpus luteum in certain doses by stimulation of pituitary LH secretion. The second possible mechanism is activation of the locally expressed GnRH receptors on endometrium and thus support the corpus luteum [22,23]. A direct effect of GnRH agonist on embryo and

implantation process is also possible. However, there's no evidence yet to support a direct effect of GnRH agonists on endometrium to improve the outcome.

In many animal studies GnRH injections have been described to support luteal phase after artificial insemination or embryo transfer [25]. The aim of this treatment is to enhance embryo survival rates by delaying the luteolytic mechanism [26]. Some studies reported significant improvements of 10-12% in pregnancy rates, while others did not [27-32]. Several human studies also suggested beneficial effects of GnRH agonist administration in addition to routine LPS with progesterone [21-24,33,34]. First, Tesarik *et al.* reported 0.1 mg triptorelin administration 6 days after ICSI as LPS in oocyte donation cycles. The authors reported significantly increased implantation rates with triptorelin when compared to placebo, but the clinical pregnancy rates were similar between the groups [21]. Pirard *et al.* investigated whether intranasal administration of buserelin could provide LPS in ART patients in a Randomized Controlled Trial (RCT). They randomized 23 patients to 5 different groups with different dosages of buserelin and concluded that buserelin may be effective in triggering follicular maturation and providing LPS in patients undergoing ART [22]. Tesarik *et al.* evaluated the effects of 0.1 mg triptorelin administration 6 days after Oocyte Pick-Up (OPU) in agonist (n=300) and antagonist (n=300) Intracytoplasmic Sperm Injection and Embryo Transfer (ICSI-ET) cycles [23]. All patients received routine LPS with recombinant hCG, progesterone and estradiol. Patients were randomized to triptorelin and placebo injections in both groups. Implantation rates (calculated as number of gestational sacs divided by number of transferred embryos multiplied by 100) were significantly increased by triptorelin injection in both GnRH agonist and GnRH antagonist cycles. However, the ongoing pregnancy (defined as pregnancy proceeding beyond 20 weeks of gestation) was significantly increased in only GnRH antagonist cycles. As the implantation rate was increased more significantly when compared to the clinical pregnancy rates, the authors concluded that GnRH agonists have a direct action on the implanting embryo by demonstrating a stimulatory effect on  $\beta$ -hCG secretion [23]. In both of the aforementioned studies a stimulatory effect on the corpus luteum function was suggested [22,23].

In another RCT, 120 IVF patients stimulated by long luteal protocol and with endometrial thickness  $\leq 7$  mm were randomized to receive LPS with triptorelin and placebo injections [24]. The study group received three sequential triptorelin 0.1 mg injections on the day of OPU, on the day of ET and 3 days thereafter in addition to routine LPS with progesterone and the control group received placebo injections in addition to routine LPS with progesterone. They found significantly increased implantation and pregnancy rates with GnRH agonist administration in patients with thin endometrium and suggested a direct effect of GnRH agonist on endometrium and corpus luteum which improves the endometrial receptivity. Razieh *et al.* assessed the effect of GnRH agonist administration as LPS in patients stimulated by long luteal protocol in an RCT and demonstrated beneficial effects single dose triptorelin s.c. injection 3 days after ET [33]. Isik *et al.* also reported increased implantation, clinical pregnancy (defined as the presence of a fetus with a heartbeat at 6th gestational week confirmed by ultrasound), multiple pregnancy and live birth rates with the addition of single dose 0.5 mg leuprolide

acetate injection 6 days after ICSI to routine LPS with 600 mg vaginal micronized progesterone in antagonist cycles [34].

However, contrary results were also achieved regarding the beneficial effects of GnRH agonist administration for LPS [17,35-37]. Ata *et al.* failed to demonstrate beneficial effects of GnRH agonist administration as LPS in patients stimulated by long luteal GnRH agonist protocol [17]. In a double-blind RCT, 570 ICSI-ET patients were randomized to receive 0.1 mg triptorelin injection or placebo 6 days after ICSI in addition to routine LPS with progesterone. The authors found similar implantation, clinical pregnancy and multiple pregnancy rates in both groups. In another RCT including 426 patients treated by long agonist protocol, subjects were randomized to receive three 1 mg doses of leuprolide acetate or placebo injections 6 days after OPU in addition to routine LPS with progesterone [27]. The implantation, clinical pregnancy and multiple pregnancy rates were similar between the study and control groups. In a recent RCT Yıldız *et al.* assessed the effects of addition of 1 mg leuprolide acetate s.c. injection, once (3 days after ET) or twice (3 and 6 days after ET), to routine LPS with progesterone in 278 infertile patients treated with long luteal GnRH agonist stimulation protocol [36]. Although they found improved implantation, clinical pregnancy and ongoing pregnancy rates with the administration of additional leuprolide acetate injections, the results did not reach statistical significance. The results were similar in between the patients taking single dose or double doses of leuprolide acetate. The multiple pregnancy rate was significantly increased with the increasing number of leuprolide acetate injections. Recently, Aboulghar *et al.* reported the results of 446 patients who were treated with long luteal GnRH agonist stimulation protocol [37]. The patients were randomized to receive daily 0.1 mg sc GnRH agonist until day of  $\beta$ hCG and to stop GnRH agonist on day of hCG injection. The clinical and ongoing pregnancy rates were similar between the groups.

Recently, Davar *et al.* reported results of the only RCT investigating GnRH agonist addition to LPS in frozen-thawed embryo transfer cycles [38]. The authors randomized 201 patients to receive 0.1 mg sc decapeptyl three days after ET plus daily vaginal progesterone and to receive justvaginal progesterone. They found any differences regarding implantation, clinical pregnancy, ongoing pregnancy and miscarriage rates. In contrast to that study, Tesarik *et al.* reported significantly increased implantation rates with GnRH agonist addition to routine LPS in oocyte donation treatment cycles and suggested enhanced developmental potential of embryo, probably by a direct effect on the embryo.

Although the mechanisms are not clear yet, GnRH agonists do not disturb the luteal phase and have stimulatory effects on corpus luteum in certain doses [22]. Most of the studies up to date evaluated the efficacy of GnRH agonists as LPS in GnRH agonist protocols [17,23,24,33,35-37]. Within those, significantly improved pregnancy rates have been proven in only two studies [24,33]. The remaining suggested beneficial effects without demonstrating statistically significant increase in pregnancy rates [17,23,35-37]. The possible mechanism of stimulating pituitary gonadotropin cells to secrete LH seems to be unlikely in down-regulated agonist cycles as the pituitary action is already suppressed [37]. To the best of our knowledge, the addition of GnRH agonists to routine LPS in GnRH antagonist cycles was assessed in only two studies and both of them suggested beneficial

effects [23,34]. Although a small sized cohort was achieved from these studies, there may be a significantly increased live birth rate with the addition of GnRH agonists to routine LPS in GnRH antagonist cycles. Because of the fact that the pituitary gland remains responsive to GnRH agonists in GnRH antagonist cycles, the addition of GnRH agonists to routine LPS may be more beneficial in GnRH antagonist cycles when compared to the GnRH agonist cycles. In addition to these data, in a recent Cochrane meta-analysis the live birth/ongoing pregnancy rate was higher in the progesterone+GnRHagonist group compared to progesterone-only group (OR0.62, 95% CI 0.48-0.81, nine RCTs, 2861 women) [39]. However, no difference was found in miscarriage and multiple pregnancy rates.

In conclusion, the effectiveness of GnRH agonist addition to routine LPS may differ between GnRH agonist and GnRH antagonist cycles. The specific group of patients that may benefit from GnRH agonist administration including frozen thawed cycles and optimal dose and timing of GnRH agonist administration should be defined in further RCTs.

## References

- Bourgain C, Devroey P, Van Waesberghe L, Smits J, Van Steirteghem AC. Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. *Hum Reprod.* 1990; 5: 537-543.
- Bulletti C, de Ziegler D. Uterine contractility and embryo implantation. *Curr Opin Obstet Gynecol.* 2005; 17: 265-276.
- Penzias AS. Luteal phase support. *Fertil Steril.* 2002; 77: 318-323.
- Rosenberg SM, Luciano AA, Riddick DH. The luteal phase defect: the relative frequency of, and encouraging response to, treatment with vaginal progesterone. *Fertil Steril.* 1980; 34: 17-20.
- Porter RN, Smith W, Craft IL, Abdulwahid NA, Jacobs HS. Induction of ovulation for in-vitro fertilisation using buserelin and gonadotropins. *Lancet.* 1984; 2: 1284-1285.
- Hughes EG, Fedorkow DM, Daya S, Sagle MA, Van de Koppel P, Collins JA. The routine use of gonadotropin-releasing hormone agonist prior to *in vitro* fertilization and gamete intrafallopian transfer: A meta-analysis of randomized controlled trials. *Fertil Steril.* 1992; 58: 888-896.
- Macklon NS, Fauser BC. Impact of ovarian hyperstimulation on the luteal phase. *J Reprod Fertil Suppl.* 2000; 55: 101-108.
- Kolibianakis EM, Bourgain C, Platteau P, Albano C, Van Steirteghem AC, Devroey P. Abnormal endometrial development occurs during the luteal phase of nonsupplemented donor cycles treated with recombinant follicle-stimulating hormone and gonadotropin releasing hormone antagonists. *Fertil Steril* 2003; 80: 464-466.
- Miyake A, Aono T, Kinugasa T, Tanizawa O, Kurachi K. Suppression of serum levels of luteinizing hormone by short- and long-loop negative feedback in ovariectomized women. *J Endocrinol.* 1979; 80: 353-356.
- Tavaniotou A, Devroey P. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. *Fertil Steril.* 2003; 80: 654-655.
- Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in *in vitro* fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. *J Clin Endocrinol Metab.* 2003; 88: 4186-4192.
- Aboulghar M. Luteal support in reproduction: when, what and how? *Curr Opin Obstet Gynecol.* 2009; 21: 279-284.
- Nosarka S, Kruger T, Siebert I, Grové D. Luteal phase support in *in vitro* fertilization: meta-analysis of randomized trials. *Gynecol Obstet Invest.* 2005; 60: 67-74.
- Soliman S, Daya S, Collins J, Hughes EG. The role of luteal phase support in infertility treatment: a meta-analysis of randomized trials. *Fertil Steril.* 1994; 61: 1068-1076.
- Daya S, Gunby J. Luteal phase support in assisted reproduction cycles. *Cochrane Database Syst rev.* 2004; 16: CD004830.
- Mochtar MH, Hogerzeil HV, Mol BW. Progesterone alone versus progesterone combined with HCG as luteal support in GnRH/HMG induced IVF cycles: a randomized clinical trial. *Hum Reprod.* 1996; 11: 1602-1605.
- Ata B, Yakin K, Balaban B, Urman B. GnRH agonist protocol administration in the luteal phase in ICSI-ET cycles stimulated with the long GnRH agonist protocol: a randomized, controlled double blind study. *Hum Reprod.* 2008; 23: 668-673.
- Fatemi HM, Kolibianakis EM, Camus M, Tournaye H, Donoso P, Papanikolaou E, et al. Addition of estradiol to progesterone for luteal supplementation in patients stimulated with GnRH antagonist/rFSH for IVF: a randomized controlled trial. *Hum Reprod.* 2006; 21: 2628-2632.
- Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. *Fertil Steril.* 2008; 90: 1685-1691.
- El-Toukhy T, Sunkara SK, Khairy M, Dyer R, Khalaf Y, Coomarasamy A. A systematic review and meta-analysis of acupuncture in *in vitro* fertilisation. *BJOG.* 2008; 115: 1203-1213.
- Tesarik J, Hazout A, Mendoza C. Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. *Hum Reprod.* 2004; 19: 1176-1180.
- Pirard C, Donnez J, Loumaye E. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. *Hum Reprod.* 2006; 21: 1894-1900.
- Tesarik J, Hazout A, Mendoza-Tesarik R, Mendoza N, Mendoza C. Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles. *Hum Reprod.* 2006; 21: 2572-2579.
- Qublah H, Amarín Z, Al-Quda M, Diab F, Nawasreh M, Malkawi S, et al. Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of =7 mm on day of egg retrieval. *Human Fertility.* 2008; 11: 43-47.
- Peters AR, Martínez TA, Cook AJ. A meta-analysis of studies of the effect of GnRH 11-14 days after insemination on pregnancy rates in cattle. *Theriogenology.* 2000; 54: 1317-1326.
- Mann GE, Lamming GE, Fray MD. Plasma oestradiol and progesterone during early pregnancy in the cow and the effects of treatment with buserelin. *Anim Reprod Sci.* 1995; 37: 121-131.
- Macmillan KL, Taufa VK, Day AM. Effects on an agonist of gonadotrophin realizing hormone (buserelin) in cattle. III: Pregnancy rates after a post-insemination injection during metoestrus or dioestrus. *Anim Reprod Sci.* 1986; 11: 1-10.
- Sheldon IM, Dobson H. Effects of gonadotrophin releasing hormone administered 11 days after insemination on the pregnancy rates of cattle to the first and later services. *Vet Rec.* 1993; 133: 160-163.
- Drew SB, Peters AR. Effect of buserelin on pregnancy rates in dairy cows. *Vet Rec.* 1994; 134: 267-269.
- Jubb TF, Abhayaratne D, Malmö J, Anderson GA. Failure of an intramuscular injection of an analogue of gonadotrophin-releasing hormone 11 to 13 days after insemination to increase pregnancy rates in dairy cattle. *Aust Vet J.* 1990; 67: 359-361.
- Ryan DP, Snijders S, Condon T, Grealy M, Sreenan J, O'Farrell KJ. Endocrine and ovarian responses and pregnancy rates in dairy cows following the administration of a gonadotrophin releasing hormone analog at the time of artificial insemination or at mid-cycle post-insemination. *Anim Reprod Sci.* 1994; 34: 179-191.

32. Szenci O, Takacs E, Sulon J, de Sousa NM, Beckers JF. Evaluation of GnRH treatment 12 days after AI in the reproductive performance of dairy cows. *Theriogenology*. 2006; 66: 1811-1815.
33. Razieh DF, Maryam AR, Nasim T. Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection. *Taiwan J Obstet Gynecol*. 2009; 48: 245-248.
34. Isik AZ, Caglar GS, Sozen E, Akarsu C, Tuncay G, Ozbicer T, et al. Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study. *Reprod Biomed Online*. 2009; 19: 472-477.
35. Inamdar DB, Majumdar A. Evaluation of the impact of gonadotropin-releasing hormone agonist as an adjuvant in luteal-phase support on IVF outcome. *J Hum Reprod Sci*. 2012; 5: 279-284.
36. Yıldız GA, Sükür YE, Ates C, Aytaç R. The addition of gonadotrophin releasing hormone agonist to routine luteal phase support in intracytoplasmic sperm injection and embryo transfer cycles: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014; 182: 66-70.
37. Aboulghar MA, Marie H, Amin YM, Aboulghar MM, Nasr A, Serour GI, et al. GnRH agonist plus vaginal progesterone for luteal phase support in ICSI cycles: a randomized study. *Reprod Biomed Online*. 2015; 30: 52-56.
38. Davar R, Mojtahedi MF, Miraj S. Effects of single dose GnRH agonist as luteal support on pregnancy outcome in frozen-thawed embryo transfer cycles: an RCT. *Iran J Reprod Med*. 2015; 13: 483-488.
39. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev*. 2015; 7: CD009154.