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Review Article

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

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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 trophectoderm 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

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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 multipled 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 ß-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 ≤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 ßhCG 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.

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