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REVIEW

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GnRH agonist as a luteal support in IVF cycle: mini-review—is there a role?

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Abstract

Background: It has been established that assisted reproductive technology (ART) cycles are usually accompanied by a defective luteal phase, and that luteal phase support (LPS) is mandatory to improve reproductive outcomes. This review aims to summarize the hypothesis, safety and current evidence about GnRH agonist as a luteal phase support in ART.

Main body: There are many regimens of luteal phase support to improve ART outcomes in women undergoing fresh and thawed cycles. Luteal phase support drugs include progesterone, human chorionic gonadotropin, gonadotropin-releasing hormone agonist, estradiol, and recombinant luteinizing hormone. There is some debate about optimal drugs and timing for start of LPS in ART cycles.

Conclusion: Although most centers support luteal phase by vaginal progesterone, GnRH agonist is a debatable drug for luteal support cycles.

Keywords: GnRH agonist, IVF cycle, Luteal support, Implantation

Background

Despite improvement in several aspects of IVF, implantation rate is still low [1]. In fact, only one-third of IVF cycles results in a live birth. Moreover, only a few numbers of all embryos transferred succeed to implant [2]. During the luteal phase in natural cycles, the corpus luteum under the effect of LH, produce progesterone hormone which induces the secretory changes of the endometrium, to facilitate implantation by increased thickness and quality [3].

Currently, the luteal phase defect in ART is due to high level of steroids leading to reduced levels of LH (known as premature luteolysis) [4]. Aspiration of the granulosa cells during ovum pickup, and the use of gonadotropin analogs (agonist or antagonist) during controlled ovarian stimulation (COS) can interfere with the production of progesterone during the luteal phase [5]. The drawbacks of luteal phase deficiency are decreased implantation rate, pregnancy rate and an increased miscarriage rate [6].

Luteal phase supplement has an important and positive effect on the reproductive outcomes of IVF cycles in comparison to no treatment [7]. The commonest forms of luteal phase supplementation is progesterone [8]. GnRH agonist as luteal phase support in ART cycles has currently been an area of research.

Methods of luteal phase support

Progesterone is considered the preferred drug for luteal phase support in ART cycles. Cochrane meta-analysis in 2015 concluded that progesterone supplement resulted in higher live birth rates when compared to placebo or no treatment [9]. The route and dosage of different progesterone formulations according to the European Society of Human Reproduction and Embryology (ESHRE) guidelines are 50 mg of intramuscular progesterone, 25 mg of subcutaneous progesterone and 600 mg of micronized vaginal progesterone, 90 mg daily for vaginal progesterone gel daily may have the same effect [10]. Progesterone

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can be started between the evening of the day of oocyte retrieval and up to day 3 post-ovum pickup [11, 12]. There is no significant difference in live birth rate among patients who discontinued progesterone at the time of the pregnancy test and those who continued progesterone administration up to 7 weeks [13].

Adding estradiol to the luteal phase showed no differences in IVF pregnancy rates in fresh cycles [14]. ESHRE does not recommend adding estradiol to progesterone for luteal phase support [10].

HCG is similar to LH and stimulate the corpus luteum to produce progesterone during the luteal phase. HCG injections as a LPS have no superior effect on live birth rate when compared to progesterone and compared to a combination of progesterone and estrogens [11]. LPS with HCG injections is associated with a higher rate of ovarian hyperstimulation syndrome [9, 15].

Recently, the effect of GnRH agonist as a method of luteal phase support in ART cycles became an aspect of research in different studies [16–19]. A single dose of GnRH agonist in mid luteal phase with the routine luteal phase support significantly increased implantation rate and take-home baby in ART cycles [7]. The benefits from GnRH agonist injection in luteal phase in ICSI cycles has been reported in many studies [20, 21].

The exact mechanisms of the effect of GnRHa as luteal phase support are unknown. GnRHa have an effect on corpus luteum, through LH [22], on endometrium [23], and on embryo [17]. GnRH receptors are also expressed with a high levels during luteal phase in both stromal and epithelial cells of endometrium [24, 25]. LH release has a beneficial effect on endometrium by stimulation of angiogenic factors, growth factors, and cytokines increasing the chance of implantation [17, 23]. GnRH receptors are also present on embryos [24]. GnRHa has a direct effect on embryos by regulation of the synthesis and release of human chorionic gonadotropin in embryos and placenta [17, 26].

GnRHa can be given by several regimens. Triptorelin can be added as a single bolus after 6–7 days after oocyte retrieval [26, 27] or 0.1 mg triptorelin can be offered every other day from the day of transferring embryos for total 5 days [28]. Also, Buserelin spray 100 Mcg can be given daily for 14 days during the luteal phase [29].

The effect of GnRHa in the first days of pregnancy is still subject of debate in many studies [30, 31]. Animal studies did not show teratogenic effects of GnRHa on embryos [30]. Up to 1998, more than 340 spontaneous pregnancies were exposed to GnRHa administration in the mid luteal phase. The incidence of congenital malformation and pregnancy loss were not different from general population [32]. GnRH depots were routinely used in many ICSI long protocol [33]. The active GnRH peptide in the depot form can be detected up to 6 and 7 weeks after their administration with no effect to the embryo [34]. Addition of GnRH-a to luteal support is relatively safe and effective [35].

In a meta-analysis, administration of GnRH-a as one dose (0.1 mg of triptorelin 6 days after oocyte retrieval) increased the implantation, clinical pregnancy rate per transfer, and ongoing pregnancy rate [26]. Another meta-analysis concluded that GnRHa administration during luteal phase increased live birth rate [22]. According to Cochrane in 2015, GnRHa improved Live birth when added to progesterone as a luteal support. Adding a single dose of GnRHa (triptorelin acetate, 0.1 mg) on day 6 after the oocyte retrieval had a similar effect as three doses of HCG [36].

In a systematic review and meta-analysis of about 20 studies including thawed cycles adding GnRHa in luteal phase increased clinical pregnancy rate in fresh and frozen thawed cycles [37]. A meta-analysis in 2020 included about 3584 cycles from 13 randomized controlled trials concluded that adding of GnRH-a for luteal support not only improved the clinical pregnancy rate, ongoing pregnancy rate, live birth rate, but also decreased the percentage of abortion [38]. In frozen thawed transfer cycles, a single dose of 0.1 mg triptorelin at the time of implantation (3 days after embryo transfer) did not increase reproductive outcomes [39].

In ESHRE guidelines 2019, current evidence indicates higher live birth rate and pregnancy rates with GnRH agonist bolus, repeated doses alone, or in addition to progesterone for LPS, but still it can only be used in the research (not recommend for practical usage).

Several weak points should be documented here regarding this review. A lot of studies were retrospective and non-randomized that may have selection bias. There were no studies evaluate the effects of GnRH-a as a luteal support on the mental or behavior development of neonates and children. Evidence from most systematic reviews and meta-analysis was of low or very low quality. Despite all these limitations, most studies support the usage of GnRHa as apart from luteal phase support. GnRHa can improve reproductive outcomes. After this review, we suggest individualized LPS could improve LBR. More research should be conducted regarding safety, risks, and long-term effects of GnRH agonist on children.

Conclusions

Luteal phase support in ART cycles is a very dynamic field. Whereas progesterone is a mainstay in current practice. GnRH agonist for luteal support needs more assessment. Probably research should focus on obstetric and neonatal outcomes in addition to live birth.

Abbreviations
ART: Assisted reproductive technology; LPS: Luteal phase support; COS: Controlled ovarian stimulation; ESHRE: European Society of Human Reproduction and Embryology.

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References

1. Wing T, Yeung Y, Chai J, Hang R, Li W, Chi V et al (2014) The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. Hum Reprod 29(11):2474–2481
2. Edwards RG (1995) Clinical approaches to increasing uterine receptivity during human implantation. Hum Reprod 10:60–66
3. Farquhar C, Roberts H (2010) Introduction to obstetrics and gynaecology, 3rd edn. Department of Obstetrics & Gynaecology, The University of Auckland, Auckland
4. Fatemi HM (2009) The luteal phase aPer 3 decades of IVF: what do we know? Reprod Biomed Online 19(4):4331
5. Smitz J, Devroey P, Camus M, Deschacht J, Khan I, Staessen C et al (1988) The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT. Hum Reprod 3(5):585–590
6. Pritts EA, Atwood AK (2002) Luteal support in infertility treatment: a meta-analysis of the randomized trials. Hum Reprod 17:2287–2299
7. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M (2011) Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev (10). https://doi.org/10.1002/14651858.CD009154.pub2
8. Jindal UN, Verma S (eds) (2013) Luteal phase support. Jaypee Brothers, Medical Publishers, London, p 622 (Rao KA, Carp HJA, Fischer F. Textbook of In Vitro Fertilization; vol.2)
9. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M (2015) Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2015:CD009154. https://doi.org/10.1002/14651858.CD009154.pub3
10. ESHRE Reproductive endocrinology guidelines group (2019) Ovarian stimulation for IVF/ICSI-Guideline of the European Society of Human Reproduction and Embryology. ESHRE, Brussels
11. Gao J, Gu F, Miao BY, Chen MH, Zhou CQ, Xu YW (2018) Effect of the initiation of progesterone supplementation in in vitro fertilization–embryo transfer outcomes: a prospective randomized controlled trial. Fertil Steril 109:97–103
12. Fanchin R, Righini C, de Ziegler D, Olivennes F, Ledée N, Frydman R (2001) Effects of vaginal progesterone administration on uterine contractility at the time of embryo transfer. Fertil Steril 75:1136–1140
13. Watters M, Noble M, Child T, Nelson SM (2019) Short versus extended progesterone supplementation for luteal phase support in fresh IVF cycles: a systematic review and meta analysis. Reprod BioMed Online 40:143–150
14. Kolibianakis EM, Venetis CA, Papanikolaou EG, Diedrich K, Tarlatzis BC, Griesinger G (2008) Estrogen addition to progesterone for luteal phase support in cycles stimulated with GnRH analogues and gonadotrophins for IVF: a systematic review and meta-analysis. Hum Reprod 23(6):1346–1354
15. Daya S, Gunby JL (2004) Luteal phase support in assisted reproduction cycles. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD004830
16. Tesarik J, Mendoza-Tesarik R, Mendoza N (2016) Gonadotropin-releasing hormone agonist for luteal phase support: the origin of the concept, current experience, mechanism of action and future perspectives. Fertil Steril 106:268–269
17. Tesarik J, Hazout A, Mendoza C (2004) Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. Hum Reprod 19:1176–1180
18. Şükür YE, Şimşir C, Özdemir ED, Sönmezer M (2016) GnRH agonist addition to routine luteal phase support in assisted reproductive technology. Austin J In Vitro Fertil 3:1024
19. Pirard C, Loumaye E, Laurent P, Wyns C (2015) Contribution to more patient-friendly ART treatment: efficacy of continuous low-dose GnRH agonist as the only luteal support-results of a prospective, randomized, comparative study. Int J Endocrinol 2015:727569
20. Isik AZ, Caglar GS, Sozen E, Akarsu C, Tuncay G, Ozbicer T et al (2009) Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study. Reprod Biomed Online 19(4):472–477
21. Razieh DF, Maryam AR, Nasim T (2009) Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection. Taiwan J Obstet Gynecol 48(3):245–248
22. Kyrou D, Kolibianakis EM, Fatemi HM, Tarlatzi TB, Devroey P, Tarlatzis BC (2011) Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis. Hum Reprod Update 17(6):734–740. https://doi.org/10.1093/humupd/dmr029
23. Sugino N et al (2000) Expression of vascular endothelial growth factor and its receptors in the human Corpus luteum during the menstrual cycle and in early Pregnancy1. J Clin Endocrinol Metab 85(10):3919–3924
24. Reshef E et al (1990) The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua*. J Clin Endocrinol Metab 70(2):421–430
25. Raga F et al (1998) Quantitative gonadotropin-releasing hormone gene expression and immunohistochemical localization in human endometrium throughout the menstrual cycle. Biol Reprod 59(3):661–669
26. Oliveira JB, Baruffi R, Petersen CG et al (2010) Administration of single dose GnRH agonist in the luteal phase in ICSI cycles: a metaanalysis. Reprod Biol Endocrinol 8:107–112
27. Check JH, Wilson C, Levine K, Cohen R, Corley D (2015) Improved implantationand live delivered pregnancy rates following transfer of embryos derived from donor oocytes by single injection of leuprolide in mid-luteal phase. Clin Exp Obstet Gynecol 42(4):429–430
28. Fusi FM, Arnoldi M, Bosisio C, Lombardo G, Ferrario M, Zanga L, Galimberti A, Capitanio E (2015) Ovulation induction and luteal support with GnRH agonist in patients at high risk for hyperstimulation syndrome. Gynecol Endocrinol 31(9):693–697
29. Bar-Hava I, Mizrachi Y, Karfunkel-Doron D, Omer Y, Sheena L, Carmon N, Ben-David G (2016) Intranasal gonadotropin-releasing hormone agonist

(GnRHa) for luteal-phase support following GnRHa triggering, a novel approach to avoid ovarian hyperstimulation syndrome in high responders. Fertil Steril 106(2):330–333
30. Marcus SF, Ledger WL (2001) Efficacy and safety of long-acting GnRH agonists in in vitro fertilization and embryo transfer. Hum Fertil 4:85–93
31. Lambalk CB, Homburg R (2006) GnRH agonist for luteal support in IVF? Setting the balance between enthusiasm and caution. Hum Reprod 21:2580–2582
32. Dolk H, Loane M, Garne E (2010) The prevalence of congenital anomalies in Europe. Adv Exp Med Biol 686:349–364
33. Orvieto R, Kerner R, Krissi H, Ashkenazi J, Rafael ZB, Bar-Hava I (2002) Comparison of leuprolide acetate and triptorelin in assisted reproductive technology cycles: a prospective, randomized study. Fertil Steril 78:1268–1271
34. Happ J, Schultheiss H, Jacobi G (1987) Pharmacodynamics, pharmacokinetics and bioavailability of the prolonged LHRH agonist Decapeptyl-SR. In: Klijn J (ed) Hormonal manipulation of cancer, Monograph series of the European Organization for Research on Treatment of Cancer. Cambridge University Press, Raven, p 249
35. Zhou W, Zhuang Y, Pan Y, Xia F (2017) Effects and safety of GnRH-a as a luteal support in women undertaking assisted reproductive technology procedures: follow up results for pregnancy, delivery, and neonates. Arch Gynecol Obstet 295:1269–1275
36. Yılmaz NK, Kara M, Hançerlioğulları N, Erkılınç S, Coşkun B, Sargın A et al (2018) Analysis of two different luteal phase support regimes and evaluation of in vitro fertilizationintra cytoplasmic sperm injection outcomes. Turk J Obstet Gynecol 15:217–221
37. Chau LTM, Tu DK, Lehert P, Van Dung D, Thanh LQ, Tuan VM (2019) Clinical pregnancy following GnRH agonist administration in the luteal phase of fresh or frozen assisted reproductive technology (ART) cycles: systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 3:100046
38. Ma X, Du W, Hu J, Yang Y, Zhang X (2020) Effect of gonadotrophin-releasing hormone agonist addition for luteal support on pregnancy outcome in vitro fertilization/intracytoplasmic sperm injection cycles: a meta-analysis based on randomized controlled trials. Gynecol Obstet Invest 85:13–25
39. Seikkula J, Ahinko K, Polo-Kantola P, Anttila L, Hurme S, Tinkanen H et al (2018) Mid-luteal phase gonadotropin-releasing hormone agonist support in frozen-thawed embryo transfers during artificial cycles: a prospective interventional pilot study. J Gynecol Obstet Hum Reprod 47:391–395

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