Luteal phase support in assisted reproduction

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1- Is luteal support needed?

The first report of the combined use of pituitary suppression and ovarian hyperstimulation in in-vitro fertilization (IVF) and embryo transfer programmes was published in 1984 (1). Since then, the advantages of gonadotrophin hormone-releasing hormone analogues (GnRHa) have been well documented; the cancellation rate has been decreased through the prevention of premature luteinizing hormone (LH) surge, follicular recruitment has improved, and the ovarian response to hyperstimulation has been better synchronized, thus facilitating the scheduling of oocyte retrieval (OR). This pituitary suppression however, results in an impaired gonadotrophin production later on, and the output of LH remains blocked for at least 10 days after cessation of GnRHa administration (2, 3). As gonadotrophins are necessary to maintain progesterone output by the corpus luteum, exogenous luteal support is mandatory. However several reports have shown that corpus luteum function and luteal phase duration are shortened in IVF cycles regardless of the protocol used for multifollicular induction. In comparing HMG either alone or with the addition of GnRH antagonist cetorolix, Tavaniotuo et al. 2001, have shown that LH concentration declines at the mid luteal phase and without luteal supplementation the corpus luteum function will be disturbed which results in a very low implantation rate (4). The induction of multiple follicle development per se could either directly or indirectly influence the duration of the luteal phase (5); the removal of large quantities of granulosa cells at oocyte retrieval may diminish the most important source of progesterone synthesis by the corpus luteum, thus disrupting the luteal phase (6). supraphysiological levels of steroids [related to the larger number of corpora lutea] during the early luteal phase could directly inhibit LH release via negative feedback actions at the hypothalamic-pituitary axis (7). A meta-analysis comparing placebo with any form of luteal support favored the addition of luteal support (8). Vlaisavljevic (2007) compared natural IVF cycles with and without luteal support and concluded that even in a natural cycle IVF a higher pregnancy rate was observed if HCG was administered after embryo transfer (9).

2- What is the best regimen for luteal support?

Human chorionic gonadotropin (HCG), progesterone, with or without estrogen have been used to support the luteal phase.

A- Is HCG superior to progesterone?

In comparing HCG and progesterone –both intramuscular (I.M.) and vaginal- a meta-analysis preformed by Pritts and Atwood (2002) found no differences (10). However, in a recent meta-analysis comparing progesterone versus human chorionic gonadotropin (hCG) alone or in combination with progesterone, it was concluded that hCG was superior to progesterone as luteal phase support with respect to pregnancy rates (8). The drawbacks of using hCG are the increased risk of ovarian hyperstimulation and, in my opinion, the other drawback stems from the long half life of hCG in the circulation (about 8 days) which can occasionally lead to erroneous diagnosis of pregnancy with its distressing psychological impact on the patient.
B-Which route of progesterone administration confers more reproductive benefit: oral, I.M. or vaginal?

While the oral route is the patients’ preference, the very high dose needed to be administered to reach a sufficient progesterone concentration in the serum will lead to several problems. The breakdown products from the metabolism of oral progesterone have been associated with sedation, drowsiness, and other hypnotic effects, as well as flushing, nausea, and fluid retention. In addition, several studies have shown the superiority of vaginal progesterone (11, 12). In comparing vaginal and I.M routes, both have side effects. Intramuscular injections are not only painful, but can also lead to inflammation and even sterile abscess formation at the injection site (13). Severe allergic reactions to the oil used as a vehicle for progesterone injections have also been reported. Acute eosinophilic pneumonia was reported (14) and can induce severe morbidity in otherwise healthy young women.

Vaginal application of progesterone has also led to some minor side-effects such as vaginal discharge and irritation. Although I.M. injections have lead to higher serum levels of progesterone, the vaginal formulations have been shown to have better synchronization effects upon the endometrium (15). This is theorized to be due to a first pass uterine effect leading to higher uterine tissue levels and lower systemic serum levels (16). In meta-analysis by Pritts and Atwood 2002, however, the I.M. route conferred higher clinical pregnancy rate (CPR) and delivery rate (DR) than the vaginal route. Unfer et al. (2004) used 17 alpha-hydroxyprogesterone caproate every 3 days (instead of the routine daily dose) versus intravaginal progesterone in IVF-embryo transfer cycles in a prospective randomized study and found the former superior (17). A drawback in I.M. progesterone is the prolongation of luteal phase despite the absence of pregnancy. Bleeding eventually occurs, but patients often feel something is wrong when no menstruation occurs and she is not pregnant. Vaginal progesterone is available in micronized form, cream and tablets. At the present no definite significant difference between the 3 forms was found, however vaginal cream is used once daily while micronized progesterone requires multiple applications (2-3 times/day).

C-When to start luteal support?

Mochtar et al. (2006) compared the effect of the onset of luteal support on pregnancy rate, and found no significant difference whether progesterone support started at hCG injection, at oocyte retrieval or at ET (18).

D-How long should luteal support be administrated?

There is no consensus regarding the duration of luteal support. Traditionally, progesterone is administrated for 8-10 weeks after positive pregnancy test, however no difference was found if progesterone was withdrawn immediately after positive pregnancy test or continued for 8 weeks. (19, 20).

E-Adding estrogen

Several investigators have noticed that the level of estrogen is low during the luteal phase in IVF cycles. The results of adding estrogen to progesterone produced conflicting data; while Gorkemli et al. (2004) found an increased pregnancy rate (21), Fatemi et al. (2006) found no differences in pregnancy rate or implantation rate (22).

CONCLUSION

At the present evidence points out the necessity of adding luteal support to any protocol of controlled hyperstimulation; even if no agonist or antagonist is used. HCG is equivalent to progesterone in efficiency but is associated with a higher incidence of hyperstimulation syndrome. Progesterone intramuscularly seems to yield a better pregnancy rate; however the side effects of intramuscular progesterone make local vaginal progesterone cream or suppository the most common form utilized by patients. Estrogen addition does not
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Luteal phase support is an integral part of assisted reproduction treatment. In natural cycles the administration of pharmacological agents to augment progesterone secretion from the corpus...
luteum or to administer the progesterone hormone itself has not been shown to improve the pregnancy outcome. However, this is not true for assisted reproduction treatment (ART) cycles. It has been long recognized that not supporting the luteal phase in women undergoing ART is associated with significantly lower pregnancy and delivery rates (1-4).

The etiology of luteal phase insufficiency in ART cycles

Defective luteal phase in assisted reproduction cycles has been attributed to adverse effects of controlled ovarian hyperstimulation, suppression of the pituitary LH release by GNRH analogues, and to depletion of granulosa cells during follicle aspiration (5-11). The latter, however, has been challenged as aspiration of the dominant follicle in a natural cycle did not result in shortening of the luteal phase or a decreased secretion of progesterone (12).

Controlled ovarian hyperstimulation (COH) has been shown to advance endometrial maturation thus disrupting the delicate mechanism of embryo-endometrium interaction (13, 14). In the setting of COH estradiol concentrations are supraphysiological due to multifollicular maturation (15). Furthermore, immediately after ovulation estradiol concentrations decrease to a greater extent due to follicular aspiration and early progesterone rise is more pronounced due to formation of multiple corpora lutea. However, Hung Yu Ng et al. did not find an adverse effect of rapidly declining estradiol levels during the mIDLuteal phase (16). Controlled ovarian hyperstimulation also may result in a short follicular phase compared to the natural cycle further augmenting the problem of defective luteal phase (17).

The use of GnRH agonists and antagonists has been implicated in the pathogenesis of defective luteal phase after IVF treatment (10, 11).

The use of agonists may result in decreased progesterone and estradiol production during the luteal phase (18). Furthermore, agonists cause significant reduction in the length of the luteal phase, impairment of GnRH secretion and premature luteolysis. Lin et al. studied progesterone secretion from granulosa-lutein cells aspirated during oocyte retrieval in agonist or antagonist cycles (19). Secretion of progesterone recovered earlier in response to stimulation with hCG in the antagonist cycles compared to agonist cycles. Furthermore morphometric characteristics and hCG localization following immunoperoxidase staining were different in agonist and antagonist cycles (20). Contrary to initial beliefs that antagonists do not disrupt the luteal phase their use has been similarly associated with lower LH levels and a shorter luteal phase (21, 22). Friedler et al. studied luteal phase secretion of estradiol and progesterone in nonconception cycles of patients stimulated with FSH combined with agonist or antagonist for suppression of the premature LH surge (22). Conception cycles were not studied to obviate the effect of endogenous hCG. The concentration of estradiol and progesterone was found to be similar in both groups thus lending discredit to the notion that antagonists do not adversely affect the luteal phase.

The most likely mechanism for luteal phase insufficiency is a disturbance of pituitary function due to the use of GnRH analogues (agonists and antagonists), possibly in conjunction with an elevated serum estradiol concentration following ovarian stimulation as a result of multiple follicular development.

Why and how to support the luteal phase

It is evident that the luteal phase is defective in ART cycles thus necessitating the administration of exogenous agents to overcome this problem. Several agents and various routes of administration are available to the practicing physician. HCG is a time honored hormone that has been and is still being used for luteal phase support. Due to the increased risk of hyperstimulation, however, it has largely been replaced by progesterone. Progesterone can be administered orally, vaginally, or intramuscularly. Several other agents have been mainly used as adjuncts to progesterone. These are hCG, estradiol, GnRH agonists, aspirin, and various others. Despite the widely adopted practice of luteal phase support there is still the need for properly designed and adequately powered randomized studies to determine the agents/s that are associated with higher implantation rates.
hCG to support the luteal phase

The initial agent of choice to support the luteal phase has been hCG, however, due to an increased risk of ovarian hyperstimulation syndrome (OHSS) it has been largely replaced by progesterone (5, 23-25). hCG is simple to use and has been associated with respectable pregnancy rates. Four studies that compared hCG administration with placebo or no treatment in ART cycles where GnRH analogues were not used showed no difference in clinical pregnancy rates (COR=1.08; 95% CI=0.67-1.73) (26-28). However, when GnRH agonists were used hCG was superior to placebo or no treatment (COR=1.94; 95% CI=1.25-3.01). Prospective randomized studies comparing hCG with progesterone have shown similar results in terms of pregnancy and miscarriage rates (29). A more recent meta analysis showed hCG to be superior to progesterone in terms of clinical pregnancy and delivery rates (30). The favorable effect of hCG may be in part due stimulation of the corpora lutea and the secretion of various growth factors and cytokines in addition to progesterone that in turn optimizes implantation (31). However, as stated previously the administration of hCG may cause OHSS even in moderately overstimulated subjects. It is generally agreed that hCG during the luteal phase should not be administered when the peak estradiol level exceeds 2500 pg/ml and there are more than 10 mature follicles at the time of oocyte retrieval (32-34).

There appears to be no consensus regarding the dosage and frequency of hCG administered to support the luteal phase. Recently hCG has been administered in small doses to overstimulated women who received GnRH analogues for final induction of follicular maturation (35). This strategy has been associated with high pregnancy rates and no cases of OHSS and may be an option for overstimulated subjects.

Progesterone to support the luteal phase

Progesterone can be administered orally, transvaginally or intramuscularly. Oral administration is not preferred due to decreased bioavailability from hepatic first pass effect resulting in low tissue concentrations of the medication (36). Furthermore, oral use has been associated with bothersome side effects that include drowsiness, flushing and nausea. Meta analysis of studies that compared oral progesterone with placebo or no treatment showed no difference in pregnancy rates (COR=1.0; 95% CI=0.77-1.44) (29). However, more recently dydrogesterone a retroprogesterone that has good bioavailability has been compared with micronized vaginal progesterone. The authors found no difference in pregnancy rates (37).

The route of choice for progesterone delivery in Europe is vaginal. Progesterone can be administered vaginally in several forms that include tablets, suppositories and gels. A relatively dated meta-analysis showed slightly decreased ongoing pregnancy rates (COR=0.73; 95% CI=0.56-0.96), however, similar clinical pregnancy rates (COR=0.82; 95% CI=0.67-1.01) when vaginal progesterone was compared with intramuscular progesterone for LPS (29). More recent comparative studies revealed similar pregnancy and delivery rates (38). Vaginal administration of progesterone may mimic more closely the physiological secretory endometrial transformation rendering implantation more efficient (39, 40). Furthermore, vaginal administration through higher local progesterone levels decreased uterine peristaltic activity at the time of embryo transfer (41). Different routes of vaginal progesterone use appear to yield similar results. Capsules, gel, and suppositories have been compared with each other that showed no difference in the studied clinical outcomes (42-44). There is no consensus on the optimal dose of vaginal progesterone that should be administered for LPS. Different dose of vaginal tablets (300-900 mg/day), vaginal suppositories (200-400 mg/day) and gel (90-180 mg) have been used with similar outcomes. Unfortunately dosage aspects of vaginal progesterone for LPS have not been studied. Itching and local skin irritation has been reported with vaginal progesterone but otherwise the drug is well tolerated and preferred by the patients.

In North America the preferred route of progesterone delivery is intramuscular. Intramuscular progesterone injections result in higher serum progesterone levels and in earlier studies were associated with higher pregnancy rates compared with vaginal progesterone (45, 46).
More recent studies showed similar outcomes compared with vaginal progesterone (38, 47). Intramuscular progesterone use is associated with painful injections, allergic reactions, and sterile abscess formation at the injection site, and more recently two cases of acute eosinophilic pneumonia (48). As with vaginal progesterone the optimal dose (50-100 mg/day) of intramuscular progesterone is not known. Due to the side effects and similar outcomes reported with vaginal progesterone we prefer the latter for LPS.

Progesterone has been combined with hCG with the aim to benefit from the best of both worlds. A meta analysis of studies that compared progesterone with progesterone and hCG showed no difference in pregnancy rates (COR=1.1; 95% CI=0.84-1.43) (29). However, OHSS rates increased significantly when hCG was added to progesterone for LPS.

**Adjuvant treatments during the luteal phase**

Several adjuvants together with mainly progesterone have been administered during the luteal phase with the aim to increase the implantation rate. The addition of ascorbic acid or prednisolone have not been found to be beneficial (49, 50). Aspirin has been advocated both to increase ovarian responsiveness and implantation. Although some studies showed increased clinical pregnancy rates with the use of aspirin during ovarian stimulation and the subsequent luteal phase others did not corroborate these results (51-54). A very recent meta-analysis of the prospective randomized studies showed that aspirin did not increase pregnancy and delivery rates in the ART setting (55).

Estrogen has been advocated as an adjuvant to progesterone for LPS. Estrogen can be administered either orally or transdermally. While two earlier randomized trials showed a beneficial effect of estrogen in terms of pregnancy rates, recent studies failed to corroborate these results (33, 56-60). One study found a significant benefit from the use of phytoestrogens and this strategy is worthwhile further exploration (61). In one other study transdermal estrogen was used and found to be beneficial (57). However, this study suffered from low pregnancy rates in the control group. Lukaszuk et al supplemented the luteal phase with 2, 4, or 6 mg of estradiol valerate and found only the 6 mg dose to be beneficial (62). In a recent study that is in press, Engmann et al. administered 4 mg estrace during the luteal phase in women stimulated with either the agonist or antagonist protocols (63). The authors found significantly decreased pregnancy rates in the long GnRH agonist group supplemented with estradiol. Our experience with oral estrogen supplementation during the luteal phase has not been favorable. A randomized study using transdermal estrogens is currently underway in our institution.

GnRH agonists have also been proposed as a novel form of luteal phase support. Two studies showed an improvement in pregnancy rates with a single dose GnRH agonist administration in mid luteal phase (64). A recent prospective randomized placebo controlled double blind study performed in our institution showed no additional benefit from the addition of GnRH agonists on progesterone for LPS in patients undergoing ICSI who were stimulated with a long agonist protocol. We believe that this seemingly simple strategy should be further explored prior to its incorporation into routine practice.

**CONCLUSION**

1. Luteal phase is deficient in women undergoing ART treatment. This is true for women stimulated with agonist or antagonists combined with gonadotropins.
2. Support of the luteal phase is essential.
3. LPS with HCG yields satisfactory pregnancy rates but carries the risk of OHSS. In selected patients, however, it is simple to use and should be given further consideration particularly in light of recent evidence that it may be more effective than progesterone.
4. Progesterone is preferred for LPS by almost all IVF centers and appears to be the current agent of choice.
5. Vaginal progesterone should be preferred as its is as effective as intramuscular progesterone and is associated with less side effects-effective and more user friendly.
6. The role adjuvants such as estrogen and GnRH analogues should be further explored.

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Lewin A, Benshushan A, Mezker E, Yanai N, Schenker JG, Goshen R. The role of estrogen support during the luteal phase of in vitro fertilization-embryo transplant cycles: a
Luteal phase supplementation or support is a common practice in IVF treatment. It significantly improves the embryo implantation rate, pregnancy and delivery rates as ovarian superstimulation during IVF is commonly associated with luteal phase deficiency. The aspiration of the granulosa cells that surround the oocyte and the use of gonadotropin releasing hormone agonists (GnRHa) during assisted reproduction technology (ART) treatment can interfere with the production, during the luteal phase, of progesterone, which is necessary for successful implantation of the embryo (1).

The second mechanism of luteal phase deficiency is caused by gonadotropin releasing hormone agonist (GnRH-a) used in the ovarian stimulation regimen to prevent premature LH surge. This results in persistent block of the LH output for at least ten days after discontinuing GnRH-a, which can result in impairment of progesterone secretion by the corpus luteum (2). This increases estrogen/progesterone ratio, which is associated with an inhibitory effect on embryo implantation.

In an attempt to enhance the probability of pregnancy, different doses, durations and types of treatments for LPS have been evaluated. There is, however, no agreement regarding the optimal supplementation scheme (3). Some authors suggested IM progesterone-in-oil as the best method of luteal phase support (4). Others suggested vaginal progesterone (5) while some claimed that both hCG and intra-vaginal progesterone are equally effective (6).

GnRH agonist was recently suggested as a novel luteal phase support. The mechanism of the presumed beneficial effect of luteal-phase GnRH agonist administration is not clear and may be due to the drug action at multiple levels. It was hypothesized that GnRH agonist may support the corpus luteum by stimulating the secretion of LH by pituitary gonadotrophin cells or by acting directly on the endometrium through the locally expressed GnRH receptors (7). Tesarik et al. (2004) evaluated 138 women who were assigned to receive a single injection of 0.1 triptorelin 6 days after ICSI treatment or to receive placebo. In their series, they reported a significantly higher implantation and pregnancy rates in the GnRH agonist treated group compared with the placebo (8).

Moreover, Pirard et al. (2005) investigating whether the intranasal administration of 100 µg of buserelin to 23 patients who underwent IVF treatment, found that E2 and P concentrations were sustained and the implantation and pregnancy rates were significantly improved with increased doses and frequency of GnRH-a administration. These findings may suggest a direct effect of GnRH agonist on the embryo (7). In a prospective randomized study, Tesarik et al. evaluated the effect of GnRH agonist (0.1 mg triptorelin)
administration in the luteal phase on outcomes in both GnRH agonist (n = 300) and GnRH antagonist (n = 300) ovarian stimulation protocols (9). They were randomly assigned to receive a single injection of GnRH agonist (study group) or placebo (control group) 6 days after ICSI. The PR were enhanced for both protocols, in long GnRH agonist protocol the clinical implantation rate were 29.8 versus 18.2% respectively (P < 0.05). Ongoing PR were 46.8 versus 38.0% respectively (P = NS). In patients treated with the GnRH antagonist protocol, clinical implantation rates were 27.1 versus 17.4% respectively (P < 0.05) and ongoing PR were 44.8 versus 31.9% respectively (P < 0.05).

Luteal-phase GnRH agonist administration additionally increased the luteal-phase serum hCG, E2 and progesterone concentrations in both ovarian stimulation regimens. It was postulated that the beneficial effect may have resulted from a combination of effects on the embryo and on the corpus luteum (9).

Despite these encouraging results, this way of supplementation was not widely adopted as great concern exists about possible adverse effects on oocytes and, more importantly, on embryos (10). However, the incidence of miscarriage and the long term follow-up of children born after inadvertent administration of GnRH-a in early pregnancy do not appear to be altered (11, 12). In order to establish a potential positive role of GnRH agonist administration in the luteal phase of stimulated IVF cycles, further large prospective trials are needed.

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