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# Luteal Phase Support in ART: An Update

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http://dx.doi.org/10.5772/51093

## 1. Introduction

Assisted reproductive techniques (ART) as defined by ICMART (international society of monitoring assisted reproduction) and WHO is all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocytes and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor [1]. On the other hand the term medically assisted reproduction (MAR) is given to the wider scope involving reproductive ovarian stimulation with or without insemination and ART techniques mentioned above [1]

The luteal phase is defined as the period from occurrence of ovulation until the establishment of a pregnancy or the resumption of menses 2 weeks later. In the context of assisted reproduction techniques luteal phase support (LPS) is the term used to describe the administration of medications with the aim to support the process of implantation.

## 2. Pathophysiology of luteal phase in ART

Progesterone and estrogen are required to prepare the uterus for embryo implantation and to modulate the endometrium during the early stages of pregnancy. In the normal luteal phase of a nonpregnant woman, steroid production peaks four days after ovulation and continues for one week until falling several days before the next menses. If pregnancy occurs, progesterone production is restored by human chorionic gonadotrophin (hCG) stimulation. Once the oocyte is released, the follicle collapses and the remaining granulosa cells, which have acquired receptors for luteinizing hormone (LH), rapidly undergo luteinisation under the influence of LH. The formed corpus luteum requires regular

stimulation by LH to maintain adequate production of progesterone [2].The absence of LH due to pituitary suppression by gonadotropin releasing hormone (GnRh) analogues deprives the corpus luteum from this LH.

In the mid-1980s, the incorporation of GnRh agonists into ovarian stimulation regimens became associated with improved outcomes after IVF and other assisted reproduction technologies. Pituitary function does not resume completely until 2–3 weeks after the end of GnRH-agonist therapy; and luteal phase support was considered essential to counter any luteal insufficiency that may have a negative impact on an early pregnancy [3 ,4]. It is well established that luteal function is compromised in IVF cycles [5, 6, 7]. The reasons for luteal phase abnormalities in ART are multiple. It has been shown that the function of the corpus luteum is compromised by the process of follicular aspiration for oocyte retrieval as granulosa cells are mechanically disrupted and aspirated. The severity of the disruption seems to be in relation to the vigorousness and the number of aspirations and therefore the number of granulosa cells that are dislodged from the membrana granulosa layer [8].It has been proved that luteal phase defect occurs in long GnRh-agonist protocol [9] and that corpus luteum deficiency as sequel of assisted reproduction techniques in general , is partially caused by aspiration of the granulosa cells and the use of gonadotropin-releasing hormone agonists. Due to the immediate recovery of pituitary gonadotrophin release just after discontinuation of the GnRH antagonists, it has been hypothesized that the luteal phase would be less disturbed in these cycles [10]. Although preliminary observations in intrauterine insemination cycles favored this contention, studies on a limited number of cases undergoing IVF demonstrated that there was a significant reduction in pregnancy rates without luteal phase support [11]. The serum LH levels in the early and midluteal phase of GnRH antagonist–treated cycles were low, regardless of the regimen used to induce oocyte maturation [12]. In the absence of luteal phase support, the area under the curve for progesterone was suboptimal and this was accompanied by premature luteolysis [13]. In nonsupported cycles, the length of the luteal phase was shortened and early bleeding occurred [14]. Based on this body of evidence, luteal phase support should be considered in IVF cycles where GnRH antagonists are used.

Other causes of the luteal phase defect observed in stimulated IVF cycles are related to the multifollicular development achieved during ovarian stimulation. This leads to supra-physiological concentrations of steroids secreted by a high number of corpora lutea during the early luteal phase, which directly inhibit LH release via negative feedback actions at the hypothalamic – pituitary axis level, rather than a central pituitary cause or steroidogenic abnormality in the corpus luteum [15].As previously alluded to, luteal phase defect in IVF is present whether GnRH agonist or antagonist is used [16]. Many meta-analyses concurred that luteal support improves IVF outcome [17, 18 ,19 ,20, 21].The most recent Cochraine review [21] confirmed earlier studies and found that luteal phase support with hCG provided significant benefit as compared to placebo or no treatment, with a significant increase in ongoing pregnancy rate and a decrease in miscarriage rate when GnRH agonist was used. Luteal phase support with progesterone, compared to placebo or no treatment in GnRH agonist and non-GnRH agonist cycles, also resulted in a significant increase in clinical pregnancy rates and live birth.

## 3. Options of luteal support in ART

To correct the luteal phase defect in stimulated IVF/ICSI cycles, progesterone and /or human chorionic gonadotrophin (hCG) can be administered. The addition of estardiol to progesterone luteal support is currently debated and the final situation in luteal phase support needs further studies. The use of GnRh agonist in luteal support has been recommended in more recent studies.

## 4. Progesterone

Progesterone produced by the corpus luteum causes the secretory transformation of the endometrium that is necessary for implantation and for the early development of the fertilized ovum. In response to progesterone, the glands become tortuous and secretory and there is an increase in stromal vascularity, thus making the endometrium both morphologically and functionally well prepared for implantation. Progesterone preparations can be divided into two groups: natural progesterone and synthetic preparations. Synthetic derivatives or progestins are 1) 17-hydroxyprogesterone derivatives and 2) 19-nortestosterone derivatives. The 19-nortestosterone synthetic derivatives resist enzymatic degradation if given orally, but have a high incidence of secondary effects and have been associated with mood changes, depression, virilization, decreases in high-density lipoproteins, luteolysis and a possibly teratogenic effect that limits their use during fertile cycles. Natural progesterone has no adverse effects on high-density lipoproteins, no teratogenic effects and is more effective than the derivatives in inducing secretory changes at the endometrium (22). Traditionally, progesterone was given by means of intramuscular injections, what makes it unacceptable for long-term treatment. In this respect the vaginal route is the preferred way to administer natural progesterone.

Various formulations of progesterone are now available, including oral, vaginal, and intramuscular (I.M) progesterone . Parenteral administration of progesterone, vaginally or I.M, does not subject the compound to the significant metabolic consequences of oral administration. Progesterone administered orally is subjected to first-pass pre-hepatic and hepatic metabolism. This metabolic activity results in progesterone degradation to its $5\alpha$- and $5\beta$-reduced metabolites [23] . Levine and Watson [24] compared the pharmacokinetics of an oral micronized progesterone preparation (Prome- trium, 100 mg, Solvay Pharmaceuticals Inc., Marietta, GA) with that of a vaginal progesterone gel (Crinone 8%, 90 mg).Results showed that the vaginal gel was associated with a higher maximum serum concentration of progesterone. Furthermore, the 24-hour area under the curve for drug concentration vs. time (AUC0–24) was higher in the group that had received the vaginal preparation. This signifies greater total progesterone exposure over 24 hours for a single dose of progesterone administered in a vaginal gel compared with a similar dose administered orally. Levine and Watson [24] concluded that the vaginal administration of progesterone results in a greater bioavailability with less relative variability than oral progesterone. There are no agreement on the standard dose of progesterone in luteal phase support. Studies have been conducted using I.M. injections

(12.5–100 mg/day), various vaginal preparations such as creams, pessaries, sustained release gel and vaginal rings, vaginal applications of oral formulations and oral preparations including micronized progesterone (600–1200 mg/day) and dydrogesterone (oral, 20–30 mg/day) [25].

## 4.1. Comparison between routes of progesterone administration

Progesterone can be administered orally, vaginally, or through I.M. injection and all these routes of administration have demonstrated characteristic endometrial histological changes [26]. Oral dosing requires a higher concentration in order to compensate for "first-pass" liver metabolism. The bioavailability of the orally administered progesterone can be as low as 10% [27].Micronized dosage forms of progesterone are utilized to increase efficiency of delivery. Micronization decreases particle size and shortens its dissolution time according to the equation of Noyes – Whitney[28].However, oral administration may result in noticeable sedative and anxiolytic effects due to progesterone metabolites that enhance inhibitory neurotransmission by binding to the GABA$_A$ receptor complex [29].

Intramuscular injections of micronized progesterone in oil result in a higher peak and longer lasting plasma concentrations when compared to aqueous solutions. But, a daily administration is required due to a rapid metabolism. Progesterone in oil (USP) is formulated with sesame oil (50 mg/ml) and 10% v/v benzyl alcohol that functions as preservative. Intramuscular injections are difficult to self-administer and are often painful. A common practice is to warm up the oil solution in order to decrease its viscosity in an attempt to reduce pain with injection [28].

Bulletti et al[30] first described a preferential trafficking of vaginally delivered progesterone to the uterus leading to a higher progesterone concentration in the endometrial tissue compared to the blood serum. Therefore, targeted delivery of progesterone directly to the uterus is thus achievable through utilizing this 'uterine first pass effect' [31] .The anatomy of the vagina with its rich vascular plexus provides an ideal environment for absorbing drugs. The rugae of the vaginal wall increase the total available surface area. The vascular system around the vagina and the venous drainage of the vagina does not initially pass through the liver, and thus bypasses the first pass hepatic effect [32] .By avoiding the hepatic first pass effect, vaginal progesterone does not create high concentrations of metabolites that cause undesired side effects. Vaginal administration of progesterone results in more consistent serum levels, which can remain elevated for up to 48

## 4.2. Oral dydrogesterone vs. vaginal micronized progesterone

In a prospective randomized study [33] a total of 430 women underwent IVF/ICSI treatment. Long protocol gonadotropin releasing hormone analogue down-regulation was followed by gonadotropin stimulation. Luteal support was initiated from the day of embryo transfer and continued for up to 14 days. Patients were randomised to luteal

supplementation with either intravaginal micronised progesterone 200 mg three times daily (n = 351) or oral dydrogesterone 10mg twice daily (n = 79). In cases of a positive pregnancy test, luteal support was continued for 12 weeks. Both dydrogesterone and micronised progesterone were associated with similar rates of successful pregnancies. Vaginal discharge or irritation were reported by 10.5% of patients given micronized progesterone. Significantly (p < 0.05), more patients given dydrogesterone than micronised progesterone were satisfied with the tolerability of their treatment. There were no differences between the treatments with regard to liver function tests. In agreement with this another study [34] compared oral dydrogesterone for luteal-phase support in assisted reproductive technologies with micronized vaginal progesterone. All patients underwent long-term downregulation with gonadotropin-releasing hormone agonists. In phase I, 498 patients were divided into three groups: long protocol and not at risk of OHSS (group A); long protocol and at risk of OHSS (group B); and those in a donor oocyte program (group C). All patients received micronized progesterone 600 mg/day, vaginally. They were also randomized to dydrogesterone 20 mg/day (n = 218) or placebo (n = 280). The pregnancy rate was higher with dydrogesterone than with placebo in group A (33.0% vs. 23.6%), group B (36.8% vs. 28.1%) and group C (42.9% vs. 15.6%; p < 0.001). In phase II, 675 patients were divided into the same three groups (groups D, E and F) and were randomized to dydrogesterone 30 mg/day (n = 366) or micronized progesterone 600 mg/day (n = 309). The pregnancy rate was significantly higher with dydrogesterone than with progesterone in group D (39.1% vs. 26.7%; p < 0.01), group E (41.2% vs. 35.6%; p < 0.01) and group F (48.2% vs. 33.9%; p < 0.001).Although both routes had more or less comparable cycle outcome the cited studies did not comment on sedative effects of oral synthetic dydrogesterone compared with vaginal micronized progesterone.

## 4.3. Micronized progesterone: oral vs. vaginal routes

A prospective randomized small sample study [35] compared the efficacy of micronized progesterone administered as luteal support following ovulation induction for in-vitro fertilization (IVF)– embryo transfer in cycles using gonadotrophin-releasing hormone agonist, orally (200 mg×4/day) or vaginally (100 mg×2/day) and to characterize the luteal phase hormonal profile during such treatments. A total of 64 high responder patients requiring intracytoplasmic sperm injection due to male factor infertility were prospectively randomized into two treatment groups. Patients treated orally or vaginally were comparable in age, number of oocytes retrieved, and number of embryos transferred per cycle. Following low dose vaginal treatment, a significantly higher implantation rate (30.7 versus 10.7%, P < 0.01), and a tendency to higher clinical pregnancy rate (47.0 versus 33.3%) and ongoing pregnancy rate (41.1 versus 20.0%) was observed, compared with oral treatment. In conception cycles, luteal serum progesterone and oestrogen concentrations did not differ between the treatment groups. In non-conception cycles, late luteal progesterone concentrations were significantly lower following vaginal treatment. As low dose micronized progesterone administered vaginally is simple, easy and well tolerated, it could be recommended as the method of choice for luteal support.

### 4.4. Oral micronized progesterone vs. I.M progesterone

Oral micronized progesterone for luteal phase support in ART not only results in significantly lower rates of pregnancy and implantation compared with those for I.M. , hCG or progesterone, but also causes more side effects [36] .In a prospective randomized study, the implantation rate was significantly lower in the oral micronized progesterone arm compared with I.M. progesterone. There was no significant difference in pregnancy rate between both groups [37] As mentioned above parenteral administration of progesterone, vaginally or I.M, does not subject the compound to the significant metabolic consequences of oral administration. Progesterone administered orally is subjected to first-pass pre-hepatic and hepatic metabolism [23].

### 4.5. Vaginal vs. IM progesterone for luteal support

Previous randomized trials [38 ,39] and a meta-analysis [18] and a Cochrane review [19] concluded that there is evidence of superiority of I.M. over vaginal progesterone for ongoing pregnancy and live birth. These studies showed that whether natural or synthetic I.M progesterone were used the results were the same : superiority of I.M. over vaginal ` progesterone For example at least two prospective randomized trials [40,41] showed that biweekly I.M. 250 mg 17-alpha hydroxyl progesterone caproate (17 –$\alpha$HPC) was superior to daily 90 mg vaginal gel. However more recent randomized trials [42 ,43] and Cochrane systematic reviews found no evidence favoring vaginal vs. I.M. administration of progesterone. The last Cochrain review and meta-analysis [21] is particularly relevant because it is the most recent (2011) and it included Sixty-nine studies with a total of 16,327 women.

## 5. Comparison of different vaginal progesterone preparations

Natural progesterone have been incorporated in different forms for vaginal adminstration.e.g. vaginal tablets or capsules , vaginal pessaries and vaginal gel. The tablets adsorb the vaginal secretions and disintegrate into an adhesive powder that adheres to the vaginal epithelium, thus facilitating sustained absorption and reduced perineal irritation [44]. Each vaginal insert delivers 100 mg of progesterone in a base containing excipients conventionally used for solid oral dosage forms: lactose monohydrate, polyvinylpyrrolidone, adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized starch, and colloidal silicone dioxide. Vaginal suppositories (e.g. Cyclogest)., contain semi-synthetic glycerides produced from interesterification of hydrogenated vegetable oil. The carrier vehicle in gel preparations (e.g. Crinone) is an oil-in-water emulsion containing polycarbophil, a bioadhesive and water-swellable polymer [28]. The water phase bypasses dependence on the local vaginal moisture, which is highly variable. The progesterone is sparingly soluble in oil (1:30 w/w) and practically insoluble in water (1:10,000 w/w) therefore the majority of the progesterone exists in a suspended form. The emulsion containing both dissolved and suspended progesterone adheres to the vaginal epithelial cells and thereafter-dissolved

progesterone permeates through the mucosal tissue. The depletion of dissolved progesterone in the formulation is replenished by the dissolution of suspended progesterone particles

## 5.1. Pessaries vs. capsules

A prospective randomized study [45] compared the luteal serum hormone level, effectiveness and tolerability of two different vaginal formulations of micronized progesterone, vaginal pessaries (Ellios) and capsules (Uterogestan) , used for luteal phase support after an in vitro fertilization (IVF). Patients received Ellios pessaries (2 times 200-mg pessary/day) or Utrogestan capsules (2  100-mg capsules, two times a day). Progesterone was administered from the day of oocyte pickup (day 0) until menses or up to 10 weeks in pregnant patients. The outcome measures showed that progesterone levels on days 0, 9, 16 were not statistically different between the two formulations. The pregnancy rate were similar in the two groups (25.5% vs. 18.6%), whereas tolerance was significantly better in pessaries` group versus capsules` group (vaginal discharge: 43% vs. 82%).

## 5.2. Suppositories vs. tablets

Another randomized trial [46] compared side effects and patient convenience of vaginal progesterone suppositories (Cyclogest) and vaginal progesterone tablets (Endometrin) used for luteal phase support in in vitro fertilization/embryo transfer cycles using pituitary. downregulation. One hundred and thirty-two infertile patients were randomized on the day of embryo transfer by a computer-generated randomization list in sealed envelopes to receive either Cyclogest 400 mg or Endometrin 100 mg twice daily for 14 days. On days 6 and 16 after ET, they rated side effects and patient convenience into four grades: none, mild, moderate and severe by completing a questionnaire.The results showed no significant differences in perineal irritation on days 6 and 16 after embryo transfer between the two groups, although there was a trend of fewer patients with perineal irritation in the Endometrin group. Significantly more patients in the Endometrin group had difficulty of administration on day 6 after embryo transfer. There were no differences in the hormonal profile on day 6 after embryo transfer and IVF outcomes between the two groups. The study concluded that there was no difference in perineal irritation after the use of Cyclogest suppositories or Endometrin tablets for luteal phase support although more patients found administration of Endometrin tablets difficult.

## 5.3. Gel vs. capsule

The first prospective randomized trial comparing vaginal cream Crinone 8% [47] investigated 126 patients undergoing cycles of IVF / ICSI. Patients received either Crinone 8% (n = 73) vaginally once daily or two Utrogest capsules (n=53) vaginally three times daily (600 mg). Clinical pregnancy rates were comparable (28.8 versus 18.9%), as were clinical abortion rates until 12 weeks of gestation (14.3 versus 10.0%) and clinical ongoing pregnancy rates (24.7 versus 17.0%) in the Crinone 8% and Utrogest groups, respectively.

Forty-seven non-pregnant patients were randomly selected to answer questions regarding comfort during luteal phase support. Crinone 8% had a clear advantage over Utrogest as it resulted in less vaginal discharge (P < 0.01) and fewer application difficulties (P<0.05). Twenty patients familiar with the alternative preparation from a previous cycle also noted that Crinone 8% was easier to apply (P < 0.01) and less time consuming (P < 0.05) to use than Utrogest. In another prospective multicenter randomized trial [48] to study the comparative efficacy and tolerability of capsules containing 200 mg of progesterone (Utrogest 200) or Crinone 8% gel for luteal phase and early pregnancy support during assisted reproduction techniques.Four hundred thirty women who underwent their first IVF or ICSI cycle were randomized after successful transfer of two or three embryos. Patients used vaginally applied capsules containing 200 mg of progesterone (Utrogest 200) three times per day or containing Crinone 8% gel twice per day. Therapy was started in the evening of the embryo transfer day and continued up to 10 weeks in pregnant women. If the pregnancy test proved to be negative, application was stopped. The luteal phase support in ART cycles with Utrogest™ 200 capsules (three times per day) or Crinone 8% gel (two times per day) by the vaginal route resulted in similar outcomes with respect to implantation, ongoing pregnancy, and abortion rates. The two recommended regimens of progesterone supplementation in ART proved to be equivalent and safe. A large prospective randomized study [49] compared the efficacy of intravaginal and I.M. progesterone for luteal phase support in IVF cycles. The study included women 25-44 years old with infertility necessitating treatment with IVF, 511 consecutive patients were enrolled; 474 completed participation, and 37 were excluded. Patient received luteal phase support using either Crinone 8% or natural progesterone in oil starting 2 days following oocyte retrieval. The outcome measure was pregnancy and delivery rates stratified by patient age. The study showed that overall, patients who received vaginal progesterone had higher pregnancy (70.9% vs. 64.2%) and delivery (51.7% vs. 45.4%) rates than did patients who received IM progesterone. Patients <35 who received vaginal progesterone had significantly higher delivery rates (65.7% vs. 51.1%) than did patients who received IMP. There were no differences, regardless of age, in the rates of biochemical pregnancy, miscarriage, or ectopics. The study concluded that in younger patients undergoing IVF, support of the luteal phase with Crinone produces significantly higher pregnancy rates than does IMP. Crinone and I.M. progesterone appear to be equally efficacious in the older patient. In a meta-analysis of published studies comparing vaginal progesterone gel for luteal support [50] seven randomized controlled trials, involving 2,447 patients, were included in the analysis. Studies were included where vaginal progesterone gel 90 mg once or twice daily versus any other vaginal progesterone form for luteal phase support. The endpoint was clinical pregnancy rate. No difference was observed in the overall clinical pregnancy rate when comparing vaginal progesterone gel with any other vaginal progesterone form. Moreover, clinical pregnancy rates were similar in protocols using only GnRH agonists and when comparing vaginal gel with the traditional treatment of 200 mg×3 vaginal progesterone capsules. The study concluded that no significant difference exists between vaginal gel and all other vaginal progesterone forms in terms of clinical pregnancy rates.

## 6. GnRh –agonist Luteal support

The first report on the place of GnRh-agonist in luteal support [51] randomized patients undergoing IVF using GnRH antagonist protocol in which triggering ovulation was done by 10 000 IU of hCG and luteal phase support was done by 600 mg of vaginal micronized progesterone as compared with triggering ovulation by 200 μg nasal GnRHa followed by different doses of intranasal GnRH-a. They found that 100 μg of buserlin intranasal three times daily is equivalent to 600 mg vaginal progesterone concerning clinical pregnancy rate. In another study [52] six hundred women about to undergo ovarian stimulation for ICSI (300 using a long GnRH agonist protocol and 300 using a GnRH antagonist protocol) were enrolled in this study. Patients treated with each of these two protocols were randomly assigned to receive a single injection of GnRH agonist or placebo 6 days after ICSI. Implantation and live birth rates were the primary outcomes.The results of the study showed that administration of 0.1 mg of GnRH agonist triptorelin on day 6 after ICSI led to a significant improvement of implantation and live birth rates after ICSI as compared with placebo. In GnRH antagonist-treated ovarian stimulation cycles, luteal-phase GnRH agonist also increased ongoing pregnancy rate. Moreover, luteal-phase GnRH agonist administration increased luteal-phase serum hCG, estradiol and progesterone concentrations in both ovarian stimulation regimens. The study concluded that luteal-phase GnRH agonist administration enhances ICSI clinical outcomes after GnRH agonist- and GnRH antagonist-treated ovarian stimulation cycles, possibly by a combination of effects on the embryo and the corpus luteum. However in a more recent study [53] five hundred and seventy women undergoing embryo transfer following controlled ovarian stimulation with a long GnRH agonist protocol were included. In addition to routine luteal phase support with progesterone, women were randomized to receive a single 0.1 mg dose of triptorelin or placebo 6 days after ICSI. Randomization was done on the day of embryo transfer according to a computer generated randomization table. Ongoing pregnancy rate beyond 20th week of gestation was the primary outcome measure. The trial was powered to detect a 12% absolute increase from an assumed 38% ongoing pregnancy rate in the placebo group, with an alpha error level of 0.05 and a beta error level of 0.2. The results showed that there were 89 (31.2%) ongoing pregnancies in the GnRH agonist group, and 84 (29.5%) in the control group (absolute difference +1.7%, 95% confidence interval −5.8% to +9.2%). Implantation, clinical pregnancy and multiple pregnancy rates were likewise similar in the GnRH agonist and placebo groups. The study concluded that single 0.1 mg triptorelin administration 6 days after ICSI following ovarian stimulation with the long GnRH agonist protocol does not seem to result in an increase ≥12% in ongoing pregnancy rates. Despite this, several independent studies reported beneficial effects of GnRh-a as luteal support. [41,42,54, 55 ,56] . In the most recent Cochrane review [15] six studies (1646 women) investigated progesterone versus progesterone + GnRH-a. The authors subgrouped the studies for single-dose GnRH agonist and multiple-dose GnRh agonist. For the live birth, clinical pregnancy and ongoing pregnancy rate the results suggested a significant effect in favor of progesterone and GnRH-a. The Peto OR for the live birth rate was 2.44 (95% CI 1.62 to 3.67), for the clinical pregnancy rate was 1.36 (95% CI 1.11 to 1.66) and for the ongoing pregnancy rate was 1.31 (95% CI 1.03

to 1.67). The results for miscarriage and multiple pregnancy did not indicate a difference of effect. The authors concluded that there were significant results showing a benefit from addition of GnRH- a to progesterone for the outcomes of live birth, clinical pregnancy and ongoing pregnancy. In another recent systematic review and meta-analysis [57] six relevant RCTs were identified including a total of 2012 patients. The probability of live birth rate (risk difference : +16%, 95% CI: +10 to +22%) was significantly higher in patients who received GnRH agonist support compared with those who did not. The subgroup analysis according to the type of GnRH analogue used for LH suppression did not change the effect observed (studies in which GnRH agonist was used during ovarian stimulation, risk difference : +15%, 95% CI: +5 to +23%); (studies in which GnRH antagonist was used during ovarian stimulation, risk difference : +19%, 95% CI: +11 to +27%). The conclusion of the study was that the best available evidence suggests that GnRH agonist addition during the luteal phase significantly increases the probability of live birth rates.

## 7. Human chorionic gonadotropins (hCG)

The use of hCG is driven by the hypothesis that, in addition to progesterone and estrogen, the corpus luteum produces other hormones which are required for endometrial transformation and optimization of the conditions for embryo implantation and development. Some randomized trials supported the use of hCG for luteal support [58 ,59].However one randomized controlled trial [60] where patients at ovum pick –up were randomized to receive luteal support as either progesterone only or hCG only or combination of progesterone and hCG showed that there were no statistically significant differences with regard to the main outcome parameter, the clinical ongoing pregnancy rate .However using a standardized discomfort scale, there were more complaints towards the end of the luteal phase in the groups receiving hCG only or an additional injection of hCG, when compared to the progesterone only groups .The conclusion of the study was that progesterone only for luteal phase support leads to the same clinical ongoing pregnancy rate as hCG, but has no impact on the comfort of the patient. Furthermore two meta-analyses [18 ,19] found no statistically significant differences in clinical pregnancy, ongoing pregnancy, and miscarriage rates between progesterone and hCG. The odds ratio of OHSS was more than threefold higher when hCG was added to the luteal phase support regimen, confirming that progesterone alone is a better strategy. In the most recent Cochrane review and meta-analysis [21], 15 studies, including 2117 women investigated progesterone versus hCG regimens. The hCG regimens were sub grouped into comparisons of progesterone versus hCG and progesterone versus progesterone + hCG. The results did not indicate a difference of effect between the interventions, except for OHSS. Furthermore subgroup analysis of progesterone versus progesterone + hCG showed a significant benefit from progesterone (Peto OR 0.45, 95% CI 0.26 to 0.79).

## 8. Estrogen

The use of a GnRH agonist is an integral part of long protocols used in IVF/ICSI cycles and it results in pituitary suppression and luteal phase deficiency with decline in serum

E2 and progesterone 8 days after hCG administration for oocyte maturation. Earlier reports indicated that serum E2 concentrations severely drop at the end of the luteal phase [61]; therefore,a concern has been raised about an additional supply of E2 during luteal phase of IVF cycles. The role of E2 luteal support is still debated after more than a decade of use. Previous meta analysis [18] and an update [62] and more recent randomized trials [63, 64] reported beneficial effects of adding E2 to luteal progesterone support. In our study [63] two hundred seventy-four women undergoing first ICSI cycles were randomized after ovum pickup into three groups of luteal support . Group I received IM progesterone only, group II received progesterone plus oral E2 valerate, group III received progesterone plus hCG. Outcome measures were pregnancy rate, implantation rate, rates of multiple pregnancy and miscarriage, and midluteal serum E2 and progesterone, and midluteal E2: progesterone ratio. The results showed that the pregnancy and implantation rates were significantly higher in group II (E2 plus progesterone) compared to group I (I.M. progesterone only) and the miscarriage rate was significantly lower in group II compared with group I. Midluteal E2 was significantly higher in group II compared with group I. The decline in E2 after ovum pickup was lowest in group II, highest in group I.

On the other hand two meta- analyses [65, 66] has shown that the addition of E2 to progesterone for luteal phase support in IVF/ICSI cycles has no beneficial effects on pregnancy rates. The last meta- analyses commented that the data in the literature are limited and heterogeneous, precluding the extraction of clear and definite conclusions. Therefore further studies are needed to clarify the exact role of E2 luteal support in long agonist vs. antagonist , normal responder vs. high responder and low responders.

## 9. Timing of starting luteal support

In stimulated IVF/ICSI cycles, the steroid production in the first week after oocyte retrieval is likely to be well timed and more than sufficient, so the start of exogenous support is not apt to be critical within this window. It was reported that pregnancy rates were higher in IVF when progesterone was started three rather than six days after oocyte collection [67] .A randomized controlled trial [68] allocated 130 patients to start luteal support at hCG day and , 128 at egg retrieval day and 127 at day of embryo transfer. Ongoing pregnancy rate of 20.8% was found in the hCG-day group versus 22.7 and 23.6% in the other two groups, respectively. This study showed that , there is no difference between the three different times of start of luteal support.

## 10. Duration of luteal support

Theoretically, progesterone would be of benefit to only 'fill in the gap' between clearance of exogenously administered hCG and the increase in endogenous hCG production. As soon as endogenous hCG production increases, the corpus luteum secretes an appropriate amount of progesterone [69].However most IVF centers extend luteal support for varying durations after positive pregnancy test. A questionnaire concerning details of luteal phase

support was returned from 21 leading centers worldwide [70]. Micronized vaginal progesterone was used in 16 centers, one center used oral micronized progesterone, three centers used 50 mg I.M. progesterone and one center used hCG. All centers started luteal phase support on day of oocyte retrieval or day of embryo transfer. Luteal phase support was stopped on the day of [beta] hCG (BhCG) in eight centers, 2 weeks after positive B hCG in four centers, 2–4 weeks after positive B hCG in five centers, at 9, 10 and 11 weeks of pregnancy in three centers and at 12 weeks in one center. Schmidt et al. [69] compared two groups of patients who used luteal phase support for 2 or 5 weeks. The ongoing pregnancy rate and the delivery rates were not significantly different. The same Danish group [71] conducted a prospective randomized study on 303 women who achieved pregnancy after IVF or ICSI. All were treated with the long protocol using GnRH agonist and given luteal support with 200 mg vaginal progesterone three times daily during 14 days from the day of transfer until the day of a positive hCG test. The study group (n = 150) withdrew vaginal progesterone from the day of positive hCG. The control group (n = 153) continued administration of vaginal progesterone during the next 3 weeks of pregnancy. The study showed that the number of miscarriages prior to and after week 7 of gestation was seven (4.6%) and 15 (10.0%) in the study group and five (3.3%) and 13 (8.5%) in the control group, respectively. The number of deliveries was 118 (78.7%) in the study group and 126 (82.4%) in the control group. The differences were not significant. This is the first randomized study to conclude that prolongation of progesterone supplementation in early pregnancy has no influence on the miscarriage rate, and thus no effect on the delivery rate and progesterone supplementation can safely be withdrawn at the time of a positive hCG test

## 11. Chapter summary

In contemporary ART, luteal phase progesterone supplementation is common practice. Various routes of administration have been developed, but most have proved to have limitations and some side effects. The use of oral progesterone is clearly inferior to intramuscular or vaginal administration and is associated with an increased rate of side effects due to its metabolites. While intramuscular delivery of progesterone continues to remain an option, an increasing number of fertility specialists prefer the vaginal route of delivery. At present, there are insufficient data for a direct comparison between intramuscular and vaginal progesterone therapy; therefore, physicians should be guided by their own clinical experience. Progesterone by whatever route or form can be started on ovum pickup day or within 48 hours, without significant differences in cycle outcome.

Luteal phase support with hCG is not superior to luteal phase support with progesterone. Supplementary administration of hCG brings no advantage when progesterone is administered . Luteal phase support with hCG increases the risk of OHSS as compared with progesterone. As yet, the role of estrogen supplementation therapy during the luteal phase of IVF cycles lacks enough evidence to be employed in routine practice. Combined luteal support using progesterone and GnRh-a showed benefit from addition of GnRH- a to progesterone for the outcomes of live birth, clinical pregnancy and ongoing pregnancy.

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