Progesterone in Assisted Reproduction: Classification, Pharmacology and Its Clinical Coorelation: A Commentary

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Abstract

The modulating effects of progesterone on endometrium structure and function are the basis for successful outcome in reproductive treatments. Considering this, progesterone has a big role in treatment of infertility and supporting the ongoing pregnancy. In this review article we have attempted to review different forms of progesterone, their metabolism in the body and the role played by exogenous as well as endogenous progesterone in assisted reproductive technologies (ART). Elevated serum progesterone levels at the end of the follicular phase in controlled ovarian stimulation (COS) leads to a poorer ongoing pregnancy rate in IVF cycles due to reduced endometrial receptivity.

Keywords: Progesterone, luteal phase support (LPS), in-vitro fertilization (IVF), Ovarian hyperstimulation (OHSS), Controlled ovarian stimulation (COS), Artificial reproductive technology (ART).

Learning objectives

- Progesterone
- Mechanism of action of Progesterone
- Classification of progesterone
- Pharmacokinetics and dynamics of progesterone
- Preparation of progesterone's
- Potential advantages of progesterone in assisted reproduction
- Cons of eleveletad serum progesterone levels in ART

Introduction

It is a natural hormone (C-21 steroid) produced mainly by the theca lutein cells of the corpus luteum. It is also secreted by the adrenal cortex in a small amount and by placenta. Progesterone produces secretory endometrium in an oestrogen-primed endometrium. Natural progesterone's are rapidly metabolised and inactivated when administered by the oral route and as such, it is to be used parenterally. Recently, a number of compounds were synthesised having properties of progesterone and could be given in a tablet form. These are called progestational agents, gestanes, progestogens or progestins.Progesterone is secreted from the luteinised theca-granulosa cells of the corpus luteum. A trace is amount is however secreted from the theca-granulosa cells of the follicle and also from the ovarian stroma.

Classification of progesterone

Pharmacokinetics and Pharmacodynamics

(Table 1) The progesterone receptor (PR) has two major forms, designated as A and B receptors [2] which differ in their molecular weight. The two forms are expressed by a single gene, the two forms are a consequence of transcription from distinctly different promoters in a complex system of transcription regulations [3]. The effects of progesterone are mediated by progesterone receptors (PR) which exert their effects mainly by regulating the expression of specific target genes. The expression of PR is oestrogen-dependent in its target tissues. Therefore, the action

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Table 1

Progesterone derivative	Progesterone content
I. Progesterone	Natural progesterone*
II. Retroprogesterone	Dydrogesterone*
III.Progesterone derivative	Medrogestone
IV. Pregnane progestogen (17 OH Progesterone derivaties)	Medroxy progesterone acetate* Megestrol acetate* Cyproterone acetate* 17 alpha hydroxyl progesterone acetate* Chlormadinone acetate*
V. Norpregnane Progestogens	Nomegesterol acetate Gestonorone caproate
VI. 19- Nor progesterone derivative	Demegestone** Promegestone** Nesterone** Trimegestone**
VII. Alkyl derivatives of 19 nor testosterone 1] Oestrane derivative 2] Gonane derivative	Norethisterone*** Lynestrenol*** Ethynodiol diacetate*** Norgestrel*** Levonorgesterol*** Desogestrel** Etonogestrel** Norgestimate** Norelgestromin** Gestodene** Dienogest**
VIII. Spironolactone derivative	Drospirenone+
IX. Unsaturated 19 nonsteroidal	Gestrinone

*No androgenic effect
** Less Androgenic Action
***High Androgenic action
+ AntiMineralocortcoid action.

of progesterone requires the priming treatment of oestrogen to induce PR.

The physiological levels of progesterone in women range from 0.23ng/ml in the follicular phase to 8.3-25ng/ml in the luteal phase and 21 to 200 ng/ml in pregnancy.

The secretion of progesterone during the luteal phase is episodic and changes closely with LH surges [4]. Progesterone is rapidly metabolised and requires frequent dosing regimen. 96.7 % of the progesterone is in a bound form and remaining is in an active from. It is metabolised in liver and excreted as sodium pregnanediol glucuronide in urine.

Progesterone can be administered orally, intravaginally, intrarectally or intramuscularly.

Oral progesterone

A systematic review and meta-analysis [5] of oral dydrogesterone and vaginal progesterone for luteal phase support showed that oral progesterone provided similar rates on live birth/on-going pregnancy and clinical pregnancy rates. Dydrogesterone is certainly a reasonable option and can be used based on the cost and side effects.

Oral preparations that are available and can be used for luteal phase support (LPS) are dydrogesterone 10 mg, three times a day, in a micronised form as 400 mg twice or thrice a day, or as medroxyprogesterone acetate 10 or 40 mg once a day.

Uterogestone is naturally available micronised progesterone

and is used orally and vaginally for LPS. Its dose for LPS is 200mg three times a day. It is used from the day of embryo transfer until at least 7 to 12 weeks of pregnancy.

A major cause of cycle cancellation during controlled ovarian hyperstimulation (COH) in women undergoing in vitro fertilisation (IVF) is the occurrence of premature luteinising hormone (LH) surges. A retrospective study [6] involving 374 patients were given human menopausal gonadotrophin (HMG) and uterogestan from day 3 of the cycle until the day of trigger showed that there is no significant difference in the mature oocyte rate, cleavage rate, clinical pregnancy rate or implantation rate. The study shows that Utrogestan is an effective oral alternative for preventing premature LH surges in women undergoing COH, which will help to establish a convenient user regimen in combination with frozen embryo transfer (FET).

In a Lotus II randomised, open centre, a multicentre trial [7] comparing 30 mg oral dydrogesterone with 8 % micronised vaginal progesterone 90mg/day for LPS confirmed that dydrogesterone may replace MVP as the standard of care for luteal phase support in fresh-cycle IVF owing to its patient-friendly oral administration route.

Intramuscular progesterone

A prospective randomised study [8] on one hundred and eighty six patients comparing progesterone in oil (100mg, IM daily), intravaginal progesterone 400mg, twice daily) and 17-αhydroxyprogesterone caproate (375mg, every three days) showed no statistical difference for biochemical, clinical and ongoing pregnancy rates.

IM progesterone is absorbed rapidly, reaching its high plasma concentrations within two hours and peak concentration within eight hours. It maintains a steady plasma concentration for up to 72 hours.

The disadvantages of the IM route include local pain and discomfort at the injection site, the risk for adverse inflammatory reactions and abscesses at the injection sites and the rare complications of a severe allergic reaction, acute respiratory distress syndrome, and eosinophilic pneumonitis, which can form three weeks after the first injection [9]. IM injection is also uncomfortable for the patient and can produce serious side effects, such as injury to the sciatic nerve with impairment of the sensory or motor function of the lower extremity [10] as well as a reaction to the oil vehicle. I.M.

Progesterone doses that can be given are, in an oil base form at doses of 12.5, 25, 50 or 100 mg daily, or as 17 alpha-hydroxy progesterone 375 mg every third day.

Lubion is an injectable preparation of synthetic progesterone. It is a water-soluble preparation. It is given as 25mg subcutaneous or intramuscular injections once a day from the day of oocyte retrieval until 12 weeks of pregnancy. This dose is equivalent to the physiologic amount of progesterone produced daily by the ovary in mid-luteal phase.

Vaginal or rectal progesterone

Vaginal administration of progesterone offers a number of advantages in terms of patient convenience and tolerability. It is a most patient friendly option, patients have the least discomfort and the greatest ease of administration with this route.

Table 2

Preparation	Indication	Dose
Crinone vaginal gel 8%	Inadequate luteal phase, ART	1 applicatorful daily
Cyclogest, Vaginal or rectal	Inadequate luteal phase, ART	200-800mg in divided dose.
Lutigest	Luteal phase support in ART	100mg 3 times/day
Utrogestan	Luteal phase support in ART	1 capsule 200mg, 3 times/day

A prospective study [11] to assess tolerability, convenience, and ease of administration of vaginal progesterone and injectable progesterone in oil given for luteal phase support was completed by infertile women diagnosed with PCOS and planning to undergo IVF found it very or somewhat convenient to insert vaginal progesterone even if it is two to three times per day.

In long agonist, IVF/ICSI-ET cycles, positive β-hCG, clinical pregnancy, and ongoing pregnancy rates do not significantly differ between normoresponder patients receiving micronised progesterone vaginal capsule (600mg/day) and those receiving progesterone vaginal gel (180mg/day) for LPS [12].

A 'first uterine pass effect' occurs when drugs are delivered vaginally, thereby providing an explanation for the unexpectedly high uterine concentrations relative to the low serum concentration observed after vaginal administration. The vaginal route permits targeted drug delivery to the uterus, maximising the desired effects while minimising the potential for adverse systemic effects [13].

Endometrial progesterone concentration reaches a steady-state within five hrs after vaginal administration [14]. Progesterone levels remain elevated for about 48 hrs with prolonged bioavailability. In a systematic review [15] of 18 RCT's comparing vaginal preparations for LPS; crinone, cyclogest, lutigest and uterogestan vaginal preparations were equally effective and safe for assisted reproductive technology cycles.

Vaginal preparations available in the UK: Progesterone for luteal phase is started from the day of ovulation or oocyte retrieval until 30 days after the positive pregnancy test (table 2).

Luteal phase deficiency and support

The luteal phase is defined as the period between ovulation and either the establishment of a pregnancy or the onset of menses usually two weeks later. Following ovulation, the luteal phase of a natural cycle is characterised by the formation of a corpus luteum, which secretes steroid hormones, including progesterone (P) and estradiol (E2). If conception and implantation occur, the developing blastocyst secretes human chorionic gonadotrophin (HCG). The role of HCG produced by the embryo is to maintain the corpus luteum and its secretions.

Luteal phase defect (LPD), or luteal insufficiency, occurs when the luteal phase is shorter than normal, progesterone levels during the luteal phase are below normal, or both.

Diagnostic tests for luteal phase deficiency are influenced by and based on the following physiologic observations:

1. Normal luteal phase length is relatively fixed at 12–14 days.

2. Progesterone levels peak in non-pregnancy cycles 6–8 days after the ovulation.

3. Progesterone is secreted in pulses.

4. The endometrial response is a reflection of the follicular phase oestrogen and the luteal-phase oestrogen and progesterone.

5. Once implantation occurs, progesterone secretion by the corpus luteum depends on rising human chorionic gonadotropin (HCG) levels.

6. Failure of HCG levels to increase directly causes corpus luteum failure and a decline in progesterone levels [17]

In the context of assisted reproduction techniques, luteal phase support (LPS) is the term used to describe the administration of medication aimed at supporting the implantation process. It is used in the fresh and frozen embryo transfer cycle in a similar way. In an attempt to enhance the probability of a pregnancy, different doses, durations and types of treatments for LPS have been evaluated. It is commenced on the day of oocyte retrieval and can be given for lengths of time that varied from four weeks until 10 to 12 weeks of a pregnancy.

Stimulated IVF cycles are associated with luteal phase defect and different doses, types and duration of LPS has been recommended. There is still no agreement regarding the optimal supplementation scheme. Both hCG and progesterone have similar effects on LPS although hCG is associated with increased risk of ovarian hyperstimulation syndrome. The supraphysiological levels of steroids during COH inducing negative feedback on the pituitary gland has been implicated for poor luteal phase support [18].

Although widely used, IM progesterone is uncomfortable and inconvenient for patients. By contrast, the vaginal progesterone gel is more convenient and easier to use. Mostly commonly used regimen is progesterone 400mg pessary twice a day or 8 % gel once a day until the day of a pregnancy test.

Stimulated intrauterine insemination (IUI) cycles

Progesterone is given one day after the HCG trigger injection or after urine LH surge. It is given most commonly as a pessary, 400 mg twice a day until two weeks or until periods whichever is earlier. In case of a missed period and a positive pregnancy, it can be stopped or continued till 12 weeks of pregnancy.

A prospective randomised controlled trial [19] of controlled ovarian stimulation with IUI in which one hundred and fourty eight women received treatment (vaginal progesterone) from the day of IUI and one hundred and fourty two women received no treatment from the day of IUI showed clinically significant pregnancy rates in the treatment group.

In a meta-analysis of five randomised controlled trials [20] comparing luteal phase support in a clomiphene citrate cycle versus gonadotrophin cycle and clinical pregnancy rate (CPR) as their primary outcome showed significantly increased CPR.

Human Chorionic Gonadotrophin as luteal phase support

GnRHa triggers to induce ovulation showed that exogenous

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progesterone administration without hCG supplementation is insufficient to obtain satisfactory pregnancy rates and that daily micro-dose hCG administration provides good LPS [21]. The luteal phase administration of human chorionic gonadotrophin (hCG) was associated with a higher incidence of severe OHSS than supplementation with progesterone alone [22]. It is likely that the longer duration of time and the greater affinity with which HCG binds to the LH receptors are responsible for the increased luteotrophic stimulation that results in the development of OHSS, particularly in susceptible women.

Gonadotrophin releasing hormone as luteal phase support

In a prospective trial [23] with serum oestradiol levels of over 2500 pg/ml after use of a GnRH agonist for triggering ovulation were randomised to GnRH agonist luteal support (0.1 mg) subcutaneously every other day) or to a control group supported by (80 μg) of recombinant human chorionic gonadotrophin (HCG) GnRH as safe and effective luteal phase support. The luteal phase support was started on day three after the embryo transfer.

Serum progesterone and ART Success

The role of progesterone elevation during the luteal phase and its impact on in-vitro fertilisation (IVF) outcome has been debatable for many years.

Patients treated with GnRH antagonists and gonadotrophins, progesterone elevation on the day of HCG administration is significantly associated with a lower probability of clinical pregnancy. Serum progesterone levels of >1.5 ng/ml are associated with lower ongoing pregnancy rates following IVF/ICSI cycles irrespective of the GnRH analogue used for pituitary down-regulation [24]. Elevated serum progesterone levels at the end of the follicular phase in controlled ovarian stimulation (COS) leads to a poorer ongoing pregnancy rate in the IVF cycles due to reduced endometrial receptivity.

High progesterone levels on the day of trigger alter with endometrial receptivity and implantation [25]. In a large retrospective study [26] involving 11,055 women who had IVF-ET and FET cycles there was an inverse correlation between implantation rate and levels of progesterone on the day of the trigger with levels of 1.5ng/l, 1.75ng/l and 2.25ng/l.

It has been suggested that a level of premature progesterone rise during the follicular phase and elevated progesterone levels (>2.0 ng/ml) before oocyte maturation were consistently detrimental to the oocyte quality [27].

In a retrospective analysis [28] of 1702 IVF/ICSI cycle Baseline (day two of the menstrual cycle) serum progesterone concentration and history of progesterone elevation (PE) are baseline variables that can predict the occurrence of PE on the day of HCG independently of the intensity of ovarian stimulation and for similar occurrence in subsequent cycles.

Conclusion

Progesterone has a big role to play in our clinical practice. Oral and Vaginal progesterone has equal benefits and is better tolerated by our patients than intramuscular preparation for luteal phase support from 7-12 weeks after confirmation of pregnancy

Conflict of interest

None to declare.

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