MEDS Public Health and Preventive Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/phpm.2022.020305
ISSN 2616-1915 Vol. 2 Num. 3

Advances in the study of luteal support in assisted reproductive technology

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Keywords: Luteal support, Luteal insufficiency, Assisted reproductive technology, Progesterone.

Abstract: Assisted Reproductive Technology (ART) is a clinically effective method of assisting pregnancy. Luteal function can be affected by down regulation and ovulation promotion during ART, so routine luteal support is an essential part of the ART process, improving clinical pregnancy and live birth rates while achieving good and stable pregnancy outcomes. At present, there is still no consensus on luteal corpus luteum support scheme and medication selection. This paper therefore discusses the dosage, dose, route, safety and efficacy of luteal support drugs in recent years to clarify the clinical significance of luteal support in assisted reproduction and to provide a reference for the clinical selection of a reasonable luteal support regimen to improve the outcome of ART assisted pregnancy.

1. Introduction

Infertility is a common condition among modern couples of childbearing age.According to WHO statistics[1,2], the prevalence of infertility in developed countries is about 8% - 12%, and in some developing countries the prevalence can even reach 30%. Globally, the incidence of infertility in China is also on the rise year by year.According to surveys [3,4], the prevalence of infertility in China has increased from 6.89% 20 years ago to about 12% - 15% in recent years, and infertility has now become the third most common disease after oncology and cardiovascular diseases. Especially since the opening up of the three-child policy, the topic of "fertility promotion" has been gaining momentum and the use of ART in clinical practice has become more widespread.In contrast, luteal insufficiency is an important cause of pregnancy failure during assisted reproduction. According to statistics [3,4], the incidence of luteal insufficiency is about 3%-10% in women of childbearing age and 3.5% in infertile women. The incidence of luteal insufficiency is 35% in patients with early pregnancy miscarriage and up to 20%-60% in patients with habitual miscarriage.Therefore, luteal support in early pregnancy has become an important treatment in ART. In this paper, we summarize the dosage, dose, route of administration, safety and efficiency of luteal support drugs in assisted reproduction technology in recent years, to clarify the clinical significance of luteal support in assisted reproduction, and also to help find a reasonable drug regimen, in order to provide a reference for clinical drug use.

2. Luteal phase defect, LPD

The corpus luteum[5] is a vascular adenoid structure that rapidly transforms after ovulation of the follicle and has the function of synthesizing steroid hormones, i.e. estrogen, progesterone and androgens.Progesterone is an essential steroid hormone during pregnancy and is involved in the secretory preparation of the fertilised egg during implantation, endometrial metamorphosis and the inhibition of uterine contractions during pregnancy. In addition, progesterone has certain anti-inflammatory and immunological effects, increasing the mother's immune tolerance to the foetus during pregnancy and preventing embryo rejection.Studies have found[6,7] that placental syncytial trophoblast cells begin to secrete progesterone after 8 - 10 weeks of gestation and that removal of the corpus luteum before 7 weeks of gestation can cause miscarriage, but that supplementation with exogenous progesterone allows the pregnancy to be maintained. Therefore, progesterone is essential during early pregnancy. Embryo transfer experiments have also confirmed[8,9] that even if the embryo is healthy and hormonally stimulated, lack of oestrogen can lead to failure of implantation or result in infertility or early miscarriage; therefore, oestrogen and progesterone work synergistically to maintain a normal pregnancy, and low oestrogen levels can also affect progesterone levels. In addition to steroid hormones, the corpus luteum also produces and secretes a large number of protein hormones, including relaxin, oxytocin and inhibin. If the corpus luteum is underdeveloped and hormone synthesis is inadequate, the above changes will not continue, predisposing to early pregnancy loss and ART failure.

LPD [10] is post-ovulatory luteal dysplasia, producing too little progesterone or premature luteal decline, resulting in reduced endometrial secretory responsiveness; the clinical manifestation is asynchronous endometrial and embryonic development, closely associated with infertility or miscarriage, the cause of which has not been fully understood to date. At present, there are no standardised and precise clinical criteria for the diagnosis of LPD. In clinical practice, luteal function is often determined by basal body temperature measurement, mid-luteal progesterone level measurement and endometrial biopsy and pathological examination.Current research suggests that the diagnosis of LPD can be confirmed by monitoring progesterone levels at the same time on days 5, 7 and 9 after ovulation, if the mean progesterone level does not exceed 15ug/ml. Once diagnosed, patients should be treated with luteal support interventions as soon as possible to improve pregnancy outcomes. Luteal support is a progesterone supplementation treatment during the luteal phase and is now widely used in ART, pre-eclampsia and recurrent miscarriage.

3. Mechanism of luteal insufficiency occurrence

During the natural menstrual cycle, the incidence of LPD in women of childbearing age ranges from 3% to 10%, and the possible mechanisms are[11]: 1. Pituitary etiology, the corpus luteum is derived from the follicle, which requires gonadotropin releasing hormone (GnRH) to secrete luteinizing hormone (LH) to stimulate follicular development, and abnormal GnRH secretion can lead to abnormal luteal function in both the luteal and follicular phases.2. pulsatile release of progesterone, which regulates follicular ovulation and granulosa cell luteinisation. abnormal LH pulse rhythms affect the synthesis and secretion of progesterone by the corpus luteum. reduced peak LH pulses and post-ovulatory LH hypopulse defects lead to luteal hypoplasia and decreased maternal hormone secretion, which in turn leads to poor endometrial transformation and affects placental formation and the ability of the placenta to produce progesterone.Inadequate secretion of follicle stimulating hormone (FSH) during the follicular phase delays follicular development and reduces estrogen secretion, resulting in inadequate feedback to the pituitary and hypothalamus, leading to LPD; 4. The hypothalamic-pituitary-ovarian axis is dysfunctional and the hormone levels are abnormal, which may also lead to LPD.

The incidence of LPD is almost 100% due to the simultaneous development of multiple corpus luteum and negative feedback suppression of LH during superovulatory cycles, the possible pathogenesis of which is: 1. The application of gonadotropin-releasing hormone agonist (GnRH-a) or gonadotropin-releasing hormone antagonist agent (GnRH-A) for superovulation during ART implementation inhibits the endogenous LH peak, resulting in endogenous LH hypersecretion and lower progesterone levels; it can also act as an inhibitor of the pituitary gland, stimulating the simultaneous development of multiple follicles, causing synthesis and secretion of estrogen and progesterone well beyond physiological amounts, negatively feedback inhibiting LH secretion, leading to luteal hypoplasia and consequently LPD.2. High doses of exogenous human chorionic gonadotropin (HCG) stimulate ovulation and then negatively reduce luteal phase LH concentration, leading to luteal insufficiency. 3. progesterone secretion, reducing the rate of embryo implantation and clinical expectancy [5]. Luteinizing insufficiency is a common clinical condition, especially after ovulation in assisted reproduction, where the incidence of LPD is 100% [12], and it is particularly important to treat luteinizing defects by supplementation with exogenous drugs. Especially in assisted reproduction, luteal support in the early stages of pregnancy is crucial in order to maintain late pregnancy and ensure a greater likelihood of success during assisted reproduction.

4. Luteal-supportive drug selection

Currently, the clinical drugs used for luteal support mainly include progesterone, HCG, GnRH-a, estrogen, etc.

4.1 Progesterone

Progesterone is a natural progestogen and is currently the drug of choice for luteal support in most fertility centres. Its mechanism of action is: (1) to promote the transformation of the endometrium from the proliferative phase to the secretory phase while preparing the fertilized egg for implantation; (2) to reduce uterine smooth muscle excitability and decrease uterine contractions to ensure stable growth of the fertilized egg and fetus in the uterus; (3) after pregnancy progesterone can promote the secretion of progesterone-induced closure factor by CD56+ lymphocytes at the mother-fetus interface to promote immune tolerance at the mother-fetus interface and prevent embryo rejection reaction. The main types of drugs include progesterone oil, micronized progesterone, dydrogesterone and progesterone vaginal delayed-release gel, etc. The routes of administration are mainly intramuscular, transvaginal and oral. Depending on the route of administration and the dose, the bioavailability of the drug varies significantly.

4.1.1 Oral progesterone

Progesterone capsules, progesterone pills and progesterone softgels (for oral use) are the three main forms of progesterone used in clinical practice. Progesterone capsules and progesterone pills are rapidly metabolised by the liver, with a peak blood concentration of 100mg taken orally in 2-3 hours and a half-life of 2.5 hours, disappearing after about 72 hours. Progesterone softgels, on the other hand, are a form of oral administration after micronisation and reach their highest plasma concentration after 1-3 hours, with a half-life of 16 - 18h and complete disappearance after approximately 72 hours, with only 10% of the dose having progestogenic activity. Although serum progesterone levels are higher than the other two oral forms, there are also problems with side effects and inadequate endothelial support [13]. Compared to intramuscular and vaginal routes of administration, oral progesterone has a relatively low incidence of fertility and pregnancy, and a significantly higher rate of miscarriage and side effects [12]. Therefore, oral natural progesterone is

now not recommended as a routine use of progesterone support in ART.

4.1.2 Intramuscular progesterone

Progesterone injection mainly includes progesterone oil and 17-alpha hydroxyprogesterone caproate, and at present, progesterone oil injection is the main form of progesterone support in China. It is most widely used in clinical practice because there is no hepatic first pass effect, high bioavailability, stable blood concentration, precise efficacy and low price. The usual dose is 20 - 60 mg/d, with peak blood concentration (Cmax 7 μg-L1) in 6 - 8 hours, lasting 48h and disappearing in about 72h [14].

However, there are serious adverse effects [15], such as injection site allergy, sclerosis, pain, abscesses and even sciatic nerve injury and drug-related lipofuscinosis [16]. With the development of technology, the administration of progesterone support is becoming increasingly diverse, and meta-studies have found[17] that vaginal administration of progesterone has similar pregnancy rates to intramuscular administration and significantly lower adverse effects.A 2017 retrospective study[18] compared vaginal micronized progesterone capsules 400 mg/d only after HCG trigger egg retrieval with GnRH-a trigger egg retrieval followed by HCG 1 The GnRH-a trigger regimen resulted in a significantly lower incidence of ovarian hyperstimulation syndrome (OHSS) and no significant difference in luteal support. It is clear that as drug dosage forms continue to improve and other delivery methods achieve similar luteal support effects as intramuscular injection, intramuscular injection will gradually be replaced.

4.1.3 Vaginal progesterone

Progesterone is the only form of progesterone that can be administered vaginally instead of intramuscularly, and is currently mainly available in the form of micronised progesterone capsules (for vaginal use) and progesterone vaginal extended-release gel. The peak blood concentration (Cmax 7-20 μg-L) is reached at 2-6 h [14]. Because of the targeted effect on the uterus, local progesterone concentrations are high and blood progesterone concentrations are significantly lower than those of intramuscular progesterone, resulting in fewer metabolites in the body and fewer systemic adverse effects. Recommended doses: progesterone vaginal extended-release gel 90 - 180mg/d; micronised progesterone capsules 300 - 800mg/d[19]. Studies have demonstrated essentially no difference in clinical pregnancy rates between 400 mg/d or 600 mg/d of micronised progesterone softgels (Angiotensin) and 90 mg/d of progesterone vaginal release gel (Snowdrop 8%) during the IVF cycle [14]. Several meta-studies have confirmed [20,21] that there was no significant difference in implantation rates, cumulative pregnancy rates and miscarriage rates between the two groups when progesterone gel 90 mg/d and progesterone injection 50 mg/d were given. In view of this, vaginal is also balanced with non-invasiveness and high local concentration, ease of use and low adverse effects, and more and more patients prefer vaginal preparations. Currently, transvaginal administration of progesterone is the preferred route of administration for ART luteal support.

4.2 Dydrogesterone

Dydrogesterone is a derivative of reverse progesterone with high selectivity for progesterone receptors, low binding to other hormone receptors, easily absorbed orally, and low adverse effects. (Overall, dydrogesterone is ideal for luteal support because of its low dose effect, high bioavailability and low hepatic load. In addition, a number of studies have shown that oral didrogestrel is safe and effective at doses of 40-80 mg per day [22]. A number of meta-analyses [23,24] have compared vaginal versus oral progestogen use, showing no statistical difference in outcome indicators, but there is still a lack of convincing evidence for the use of deferiprone alone in assisted reproduction. It is also

because the entire action of dydrogesterone is mediated with progesterone receptors and does not bind to androgen or oestrogen receptors that in 2015 the Chinese Society of Reproductive Medicine[25] suggested that oral medication alone is not recommended for luteal support and that dydrogesterone is generally used in clinical practice as an adjunct in ART in combination with other progesterone preparations.

4.3 Estrogen

Although estrogen is not an essential hormone for pregnancy, it plays an important role in maintaining the endocrine process in the uterus and inadequate estrogen production can lead to infertility or early pregnancy miscarriage [26]. The combined effect of estrogen/progestin during the luteal phase theoretically makes the endometrium more suitable for embryo implantation, but retrospective studies have confirmed[27] that there is no statistical difference in clinical pregnancy rates in the progestin-only group compared with the estrogen-added group. It has also been suggested[28] that the addition of oestrogen may have a greater role in the antagonist regimen as the luteal phase has lower oestrogen levels following the antagonist regimen. Current guidelines recommend the addition of oestrogen in the luteal phase in cases of oestrogen deficiency or lack of oestrogen and do not recommend the addition of oestrogen in fresh cycles, frozen-thawed embryo transfers in natural cycles or in spontaneous pregnancies.

4.4 Gonadotropin releasing hormone agonist (GnRH-a)

GnRH-a has a bidirectional regulatory function. Under normal conditions, GnRH-a enters the anterior pituitary through the hypothalamic-pituitary system and causes a pulsatile release of gonadotropins from the anterior pituitary, which stimulates the secretion of LH and FSH and regulates the reproductive and endocrine systems in the body [29,30]. Studies have found[31] that mid-luteal administration of GnRH-a can promote HCG secretion from the embryo in early pregnancy on the one hand, and LH secretion from the pituitary gland on the other, which in turn promotes the synthesis of oestrogen and progesterone and facilitates embryo implantation and development, closer to the natural cycle and without increasing the risk of OHSS. However, it is not suitable for patients who have suppressed pituitary function with long-acting and long-regulated regimens[32]. Some studies have reported that GnRH-a can cause abnormal luteal function[33] and affect embryo implantation, so the safety of GnRH-a in the luteal phase remains controversial.

4.5 HCG

The molecular structure of HCG is highly similar to that of LH and, after binding to LH receptors on ovarian granulosa luteal cells and membrane luteal cells, stimulates continuous secretion of endogenous progesterone and estradiol from the corpus luteum to maintain luteal function. Several studies have confirmed [34,35] that there is no significant difference between HCG and progesterone in ART luteal support in terms of embryo implantation rate, clinical pregnancy rate, live birth rate and miscarriage rate, while the incidence of OHSS is significantly higher with HCG than with progesterone. Therefore, HCG is now not recommended as a routine agent for luteal support in ART ovulation cycles [25].

5. Protocol and timing of luteal support

Several studies have confirmed [36,37,38] that the use of luteal support during ART can significantly increase the clinical pregnancy and live birth rates, therefore luteal support is often given on the day

of egg retrieval or 3 days after egg retrieval for IVF-ET, ICSI, PGD and other procedures. The doses of progesterone vaginal extended-release gel 90 - 180mg/d, progesterone capsules 300 - 800mg/d, progesterone injection 20 - 60mg/d, and dydrogesterone 10 - 20mg/d. Dydrogesterone at doses of 40 - 80mg per day still has a good safety and efficacy. The appropriate dosing regimen can be chosen on a case-by-case basis. If pregnancy is successful, luteal support is continued until 10 weeks' gestation and the dose is tapered off [39].

During ART, the timing of exogenous progesterone supplementation for luteal support is crucial due to the decrease in granulosa cells after ovulation and egg retrieval, insufficient luteal function and inadequate progesterone secretion to maintain a normal pregnancy.The 2016 Chinese Expert Consensus[40] recommends that the best time to start ART luteal support is on the day of egg retrieval or early the next morning for hormone replacement cycle resuscitation transfers Support differs slightly from ovulation or egg retrieval: start medication 3 - 4 days prior to transfer if transferring D3 frozen embryos, or 5 - 6 days prior to transfer if transferring D5 frozen blastocysts.

The duration of luteal support is not yet uniform. Theoretically, after fertilisation of oocytes before 12 weeks' gestation, the ovarian corpus luteum continues to develop into the gestational corpus luteum in response to HCG secreted by embryonic trophoblasts, which secretes progesterone and oestrogen to maintain pregnancy. The placenta gradually replaces the gestational corpus luteum in the production of steroid hormones after 12 weeks of gestation, after which the corpus luteum gradually atrophies to complete degeneration[41]. Therefore, luteal support is usually recommended from 10 - 12 weeks' gestation. A retrospective study[42] found no significant difference in clinical pregnancy or miscarriage rates between early discontinuation of luteal support and continuous users, and a shorter duration of luteal support may be a trend in the future, taking into account economic effects and patient needs.

Clinical studies [10] suggest that luteal support can be discontinued depending on the patient's condition: 1. urinary hCG(-) after 2 weeks of luteal support; 2. no pregnancy with normal menstruation; 3. normal pregnancy on ultrasound, continued until 10 - 12 weeks of gestation (serum progesterone >30ng/ml must be maintained with an increasing trend); if ultrasound indicates an abnormal pregnancy, the drug should be discontinued promptly; 4. 4. Patients with pre-eclampsia should continue the medication for 1 - 2 weeks after clinical symptoms have resolved and ultrasound shows viable embryos, or until 8 - 10 weeks of gestation; if clinical symptoms continue to deteriorate and miscarriage is inevitable, discontinue the medication and terminate the pregnancy; 5. Patients with recurrent miscarriage may be offered luteal support until 1 - 2 weeks after the gestational week of the previous miscarriage; 6. Patients with a history of late recurrent miscarriage may take the medication until 28 weeks of gestation. 6. Patients with a history of late recurrent miscarriages may take the medication until 28 weeks of pregnancy.

6. Summary

Progesterone is essential for the establishment and maintenance of pregnancy, and a range of changes due to luteal insufficiency can lead to ART failure, so even appropriate luteal support during assisted reproduction can be beneficial for ART outcomes. At present, the incidence of OHSS is significantly higher with HCG, so it is now rarely used as a luteal support option, and progesterone capsules are not routinely used for luteal support because of their significantly lower bioavailability and higher side effects than other dosage forms. Oral dydrogesterone is an optional option to supplement luteal function during ART. Progesterone injection is now widely used in clinical practice because of its low price and high blood concentration, but there are also disadvantages such as inconvenient injection, many side effects and patient pain. In the future, vaginal administration of progesterone will be the trend. In contrast, the addition of oestrogen and GnRH-a is considered

beneficial in some cases and needs to be chosen on a patient-by-patient basis. In addition, current national guidelines recommend that progesterone support during assisted reproduction be administered orally in combination with vaginal administration/injections until 10 - 12 weeks of gestation. The dosage should be reduced and discontinued according to the patient's individual circumstances. However, the best luteal support regimen should be selected on a patient-specific basis.

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