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Short Commentary

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Rectal progesterone in ART cycles as luteal phase support, is it efficient?

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Abstract

Assisted reproductive cycles have been associated with deficient luteal phase which was extensively researched. Progestogens can be given IM, SC, orally, rectally, transdermal or vaginally. Although progesterone supplementation represents the most preferable drugs for luteal phase support in fresh cycles, there is still debate which is the best time, dose and route for administration. Vaginal route is the most used in the luteal phase. Some of the clients who are using vaginal progesterone reports uncomfortable. We tried to review whether the rectal progesterone could be effective as luteal phase support and tolerable with less discomfort or not.

Keywords: IVF cycle; Luteal support; Rectal progesterone.

Introduction

Luteal phase is usually deficient in Intracytoplasmic Sperm Injection (ICSI) cycles [1]. This deficiency usually occurs in both GnRH agonist and antagonist protocols due to suppression of pituitary LH secretion [2,3] and so, the corpus luteum may be dysfunctional, causing abnormal secretion of progesterone, leading to impaired implantation and decreased pregnancy rates. Also, supraphysiological steroid hormones levels, which is related to multifollicular development and subsequent corpora lutea affect luteal phase [4,5].

Aspiration of the granulosa cells during oocyte pickup can affect progesterone production by corpus luteam [6]. So luteal phase support is very important in controlled ovarian stimulation. Both HCG and progesterone can be used for luteal phase supplementation [7].

The Practice Committee of the American Society for Reproductive Medicine concluded that luteal phase support by progesterone during assisted reproductive cycles leading to higher pregnancies, also decreasing the incidence of Ovarian Hyperstimulation (OHSS) when compared to Human Chorionic Gonadotropin (HCG) support [8].

Progesterone formulas include rectal, vaginal, oral, subcutaneous and intramuscular [7]. Intramuscular and vaginal routes considered as the commonest two methods of progesterone administration.

Different routes of progesterone can be used as luteal phase support in ART cycles and the rectal route socially accepted and also an area of research.

Luteal phase supplement has a critical role to increase the reproductive outcomes of ART cycles comparing to no treatment [7]. The most common used drug as a luteal phase support is progesterone [19].

Rectal administration of drugs may represent an alternative to oral or vaginal route and can be used for both local and systemic actions. Rectal drugs can be self-administered by patients without the need for some help from medical persons in comparison to parenteral (intramuscular – intravenous) drugs [9,10]. This is a very good option especially in developing countries and rural areas were medical persons deficient [9-11].

Drug absorption from the rectum can be transported to the liver if the drug located in the upper part of the rectum through

the portal circulation and so first-pass metabolism will occur, but absorption in the lower rectum occurred directly to the systemic circulation [12-16].

Rectal route can be affected by Pathological conditions (Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS), hemorrhoids, anal fissures) that can affect the efficacy of rectal drugs [17].

Plasma levels of progesterone were similar after vaginal and rectal administration despite the different routes of administration, and rectal administration is an alternative to vaginal progesterone [18].

Type of progesterone and route of administration

Progesterone can be used vaginal, Intramuscularly (IM), subcutaneous, intranasal, transdermal, oral or rectal, with different pharmacokinetics of progestins [7,9,18].

Vaginal progesterone offering an effective luteal phase support in ICSI cycles after which serum progesterone concentrations may be lower than intramuscular injections, but endometrial progesterone levels are higher because of the effect of uterine first pass effect [20].

Vaginal route of progesterone is preferred than oral route due to the rapid absorption and absent first-pass metabolism [21,22]. However, vaginal administration of progesterone can affect female genital tract by vaginal irritation, discharge and bleeding [7].

Progesterone as Intramuscular (IMP) injections one of the most common forms that used as luteal phase supplement, however the injections can be leading to pain, infection and abscess and may eosinophilic pneumonia as a critical systemic disorder. Also, the need to other persons for administration [23,24].

Intranasal progesterone has a bad effect (unpleasant taste of the spray) [18]. Progesterone levels in this route associated with low and insufficient level to make endometrial changes [25].

Subcutaneous Progesterone (SC) can be used as a good alternative as luteal phase support [26,27]. SC progesterone 25 mg daily progesterone can induce suitable changes for pregnancy in the endometrium [28]. SC is more convenient than intramuscular progesterone.

Transdermal route for progesterone administration is not approved by the FDA. There were no progesterone formulations approved for systemic use. And so, this route can't be used in clinical practice [29-31]. Dydrogesterone is an oral progesterone, with a better bioavailability and a good affinity to Progesterone receptors [32,33]. Lotus I and Lotus II both were randomized clinical trials concluded that oral dydrogesterone is safe, effective and tolerable as luteal phase support [34,35].

Rectal progesterone

Small numbers of clinical studies have shown that rectal progesterone is effective as micronized vaginal progesterone in supporting pregnancy in cases of ICSI cycles.

Several studies evaluate rectal administration of progesterone [36-41] progesterone levels after rectal administration were variable according to the dose, after 25 mg suppository (P4 level, 6.4 ng/mL), after 100 mg suppository (22.5 ng/mL), and after 200 mg suppository (20.0 ng/mL) [42,38].

The peaks of the progesterone level occurred after 6 to 8 hours and then gradually decrease [43]. In spite of rectal administration is considered as parenteral route, it still be subjected to some first-pass metabolism [43].

Chakmakijan and Zachariah in 1987 studied the bioavailability of micronized progesterone by measuring progesterone level in the serum after a single bolus that was given in a different route, sublingually, orally, vaginally and rectally. Rectal administration resulted in a high serum progesterone concentration twice as other forms [44].

Another prospective study includes about 442 women treated by ART All patients received rectal progesterone 400 mg daily until the pregnancy test, that's mean the efficacy and tolerability of the rectal route of progesterone [45].

A randomized comparison between vaginal and rectal route of micronized progesterone according to the efficacy, side effects and patient convenience when used as luteal phase supply in ICSI Treatment, the findings of this study concluded that there are no significant differences in the hormonal profile in the LPS and ICSI outcomes between the two routes. Patients in the vaginal route had perineal irritation and discharge, but patients who use rectal progesterone experienced rectal discomforts such as itching, tenesmus and diarrhea. However, women who had experienced both routes of administration, most of them preferred rectal route [46].

There was a systematic review concluded that there were no significant differences in miscarriage rate and multiple pregnancy rate and showed no differences between vaginal or rectal administration versus oral administration, nor between IM and oral or between vaginal and rectal routes in terms of live birth, ongoing pregnancy and miscarriage rates [7].

Another a systematic review and network meta-analysis include about 89 RCT about 29,625 women comparing 14 interventions or placebo/no luteal phase support. This review concluded that the placebo was significantly less efficient than any Luteal phase supplement (except for rectal or subcutaneous progesterone) in terms of ongoing pregnancy rate and clinical pregnancy. There were no significant differences in the acceptability profiles between different routes of administration of progesterone, and the best route cannot be uniformed for all women [47].

Another RCT conclude that Rectal route for progesterone administration as a luteal phase support is effective and well accepted alternative to vaginal route [48].

Progesterone as rectal supplementation was accepted according to the cultural background and social situations in cases that fear from vaginal progesterone. In addition, more patient comfort and compliance with the rectal route. It may also minimize any possibility of vaginal infection [49].

Limitations and weakness

Several weak points should be documented here regarding

this review. Numbers of studies were small with heterogeneity. Also, RCTs were small in number. Most of the studies report side effects subjectively without clinical examination of the patients. Despite of these limitations, most studies support the usage of rectal progesterone as an efficient route for luteal phase support. More research should be conducted regarding side effects, efficiency and patient preference about the route of progesterone supplementation.

Conclusion

Although progesterone represents the preferred drug for luteal phase supplementation in fresh ICSI cycles, there is still debate, which is the best route (orally, vaginal, rectally, injectable) for administration. There is a need to provide an efficient, well tolerated, and easy to use luteal phase support in order to improve patient satisfaction and compliance among women undergoing ART. There is a need for patient-friendly luteal phase support. Vaginal and intramuscular progesterone still the most commonly used routes for luteal phase support, although other routes as rectal route starting to be used by some centers nowadays. So, there is a need for more studies to know the best route and patient acceptability, cost-effectiveness and outcome of luteal support with progesterone formulas. Progesterone as a rectal route for supplementation was accepted socially in women who are afraid from vaginal progesterone administration. Side effects of rectal route were tenesmus and rectal itching.

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