THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (January–February 2015) 65(1):5–10
DOI 10.1007/s13224-014-0634-0

INVITED REVIEW ARTICLE

Progesterone Vaginal Ring for Luteal Support

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Received: 4 September 2014 / Accepted: 7 October 2014 / Published online: 5 November 2014

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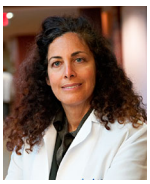

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Abstract Progesterone supplementation is universally used and has been shown to be beneficial in supplementation of the luteal phase in IVF. There are multiple options and the most commonly used include intramuscular and vaginal progesterone. A progesterone vaginal ring is a novel system for luteal support with advantages of controlled release with less frequent dosing. This review examines options for progesterone luteal support focusing on the rationale for a progesterone vaginal ring. Pub-med search of the literature. A weekly vaginal ring, although not yet FDA approved, is an effective and safe alternative for luteal supplementation in IVF. Large prospective clinical trials are needed to determine the best protocols for replacement cycles.

Keywords Luteal support · Progesterone supplementation · Progesterone vaginal ring · IVF

Introduction

The luteal phase of a natural cycle is essential for the early embryo at the blastocyst stage to implant. The corpus luteum produces the progesterone necessary for transforming

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the uterine lining and allows signaling of the embryo. The developing blastocyst secretes human chorionic gonadotropin (hCG), and in the endometrium progesterone is the essential hormone involved. Progesterone supplementation has been commonly used in women with recurrent miscarriages and women undergoing controlled ovarian hyperstimulation [1].

IVF has become a commonplace procedure since the birth of Louise Brown in 1978, and our center had the first IVF success in the US with Elizabeth Carr in 1982. The first IVF pregnancies were in natural cycles, but the Jones Institute introduced gonadotropin stimulation to increase the efficiency of the procedures. Now IVF has become routine in the US with 300,000 cycles per year [2], and gonadotropin treatment is the standard of care. The success rates have been improving with 35 % pregnancy rates per embryo transfer. Luteal supplementation with progesterone is commonly initiated 1 or 2 days after the oocyte retrieval [2].

The luteal support ensures an adequate progesterone level to prime the uterus for implantation, and to sustain the pregnancy after implantation. Successful implantation of the transferred embryo relies upon the synchronization of the patient's endometrial developmental stage with maturity of the embryonic developmental stage. Achieving this synchronization involves progesterone supplementation.

There are two main protocols for IVF. Either a gonadotropin releasing hormone (GnRH) agonist or GnRH antagonist is used in conjunction with the ovarian stimulation regimens to prevent premature LH surge and ovulation prior to the oocyte collection. Both protocols are associated with improved outcomes after IVF. Up to 15 % of IVF cycles had premature LH surges prior to the use of these medications, and these protocols with GnRH agonist and antagonist have been shown to increase the number of oocytes retrieved in a single IVF cycle increasing the total reproductive potential of the cycle. GnRH agonists have been used since the mid 1980s and GnRH antagonists since the 1990s. However, both GnRH antagonists and GnRH agonists have been shown to decrease the endogenous progesterone production in the corpora lutea and may create an iatrogenic luteal phase defect (LPD) [1]. Aspiration of granulosa cells during the oocyte pickup may interfere with the production of progesterone. In addition, the GnRH agonist works by long-term suppression of pituitary LH due to the downregulation of the receptors. This effect may last weeks after the completion of treatment. This may lead to abnormal and inadequate progesterone and estrogen secretion and may affect endometrium during implantation. With successful fertilization, implantation occurs 6–7 days after ovulation [3, 4]. Maintenance of the developing trophoblast also requires adequate levels of progesterone from the corpus luteum until the seventh or 8 week of gestation, at which time the placental production of progesterone predominates [4, 5]. Removal or failure of the corpus luteum prior to the luteal placental shift can result in early pregnancy loss during spontaneously conceived cycles [6].

It has been known since early days of IVF that stimulated IVF cycles have abnormal luteal phases, although the exact etiology for this defect remains elusive [7]. The most popular theory was that the aspiration of the granulosa cells affected the levels of progesterone. However, various studies have demonstrated that follicular remnants post-aspiration are capable of steroidogenesis [5, 6, 8]. In addition, a study by Kerin et al. showed that aspiration of preovulatory oocytes in natural cycles did not result in an apparent LPD, so the suggested mechanism for LPD following multiple follicle aspiration is more likely related to the use of GnRH agonist itself [9].

The study by Smitz et al. shows that GnRH agonists may be responsible by causing a delay in pituitary recovery of up to 10 days, and this may be one of the reasons for the LPD [10]. However, LPD was found to be present in the large majority of stimulated IVF-ET cycles before the introduction of the GnRH agonist.

The other common protocol for IVF is the use of GnRH antagonists, which are competitive inhibitors of pituitary LH, and therefore the effect is shorter acting. The study by Albano et al. was the first of several studies indicating the presence of LPD with antagonist protocol [11]. The studies on GnRH antagonists obviate the theory of prolonged pituitary suppression by GnRH agonists as the main cause of LPD in IVF-ET cycles. Another theory postulated is that the supraphysiological levels of estrogen and progesterone due to ovarian hyperstimulation during IVF lead to endometrial changes. Estradiol inhibits both FSH and LH via negative feedback inhibition at the pituitary level [3, 5, 6, 8]. This decrease in LH may effect the endometrial transformation resulting in an inadequate and out of phase endometrium, which in return may affect implantation and pregnancy rates [5, 6].

Frozen-thawed embryo transfer (FET) cycles and donor–recipient cycles require complete exogenous replacement of corpus luteal steroid production due to the absence of corpus luteum during these protocols. As opposed to stimulated IVF cycles, in donor oocyte and FET cycles, the recipients have little or no ovarian function, so there is no endogenous source of progesterone production. Progesterone replacement is essential in these patients, and they are assumed to need more progesterone than a supplemental dose. Without the administration of exogenous progesterone, pregnancy will not occur [12]. In 2011, over 15,000 donor oocyte cycles of were performed in the US with high success rate of 50 % per transfer due to the young age of the oocyte [2].

Luteal phase support with progesterone is the standard of care for assisted reproductive technology cycles and has been shown to be beneficial by the Cochrane Review (2011) [3]. The hormones used for luteal support include estrogen, progesterone, and hCG. Benefit of estrogen supplementation lacks evidence. A 1994 study was the first meta-analysis to show that the use of hCG or progesterone led to significantly higher pregnancy rates than placebo [5]. hCG is infrequently used because it leads to a higher risk of ovarian hyperstimulation syndrome. Progesterone support is universal and can be administered in intramuscular (IM), oral, and vaginal forms. [4–6]. Progesterone is commonly continued throughout the first trimester of pregnancy until the placenta fully takes over hormonal production, although progesterone supplementation continuing beyond a positive serum pregnancy test may not be needed. In a randomized controlled trial, Kohls et al. compared stopping vaginal progesterone at 5 weeks gestation versus 8 weeks gestation, resulting in no difference in live birth, or miscarriage rates between the groups [13]. The arm that stopped progesterone supplementation at 5 weeks gestation had higher rate of first trimester vaginal bleeding that was statistically significant although it did not affect birth or miscarriage rates. Most programs continue the progesterone until at least a positive fetal heart is documented on ultrasound [14].

There are multiple options for luteal support, such as IM, vaginal, and oral progesterone. Casper et al. reported that in some women who fail to achieve a pregnancy despite transfer of good quality blastocysts, the endometrium in the midluteal phase was out of phase by more than 2 days, while in others, failure to achieve pregnancy was associated with increased uterine wave activity [15]. It is known that estrogen increases uterine contractility and progesterone decreases it. The efficacy of progesterone administration may be related to a decrease in the contractility of the uterus and needs to be further evaluated.

Rationale for Vaginal Ring

As discussed above, vaginal and IM progesterone are considered to be the agents of choice as hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) [4–7]. Oral progesterone route is ineffective, requiring high dosing, resulting in less active metabolites secondary to a hepatic first-pass effect [1, 8, 16–18]. Oral formulations appear to be clinically inferior for luteal support, whereas intramuscular and vaginal preparations lead to comparable rates of implantation and clinical pregnancy. Intramuscular progesterone is painful at injection sites but provides higher serum levels of progesterone compared to vaginal and oral forms. It is also associated with normal luteal endometrial development [19, 20].

The vagina is an optimal organ for the administration of progesterone [1, 3, 4]. Due to the high permeability of the vaginal epithelium to the progesterone and easy administration of vaginal products, continuous drug release with lower daily doses is possible resulting in both systemic and local effects [20, 21].

Vaginal administration of progesterone has many advantages. The main advantages of vaginal administration are the ability to bypass hepatic first-pass metabolism, and avoid gastrointestinal absorption leading to less side effects [19]. The natural micronized progesterone can be used. This product has decreased particle size, increased surface area, and improved absorption. These characteristics result in exponential rise in bioavailability with decreased metabolic and vascular side effects [22]. The vaginal route results in higher local levels in the uterus. This is known as the 'first uterine pass effect.' Studies report higher tissue levels of progesterone despite lower serum levels compared to IM administration [22]. In RCT trials, vaginal administration has been shown to be as effective as IM administration and more effective than oral route [19, 23]. Given the equivalent efficacy, the advantage of avoiding the injection site pain and inconvenience is desirable. In general, most of vaginal products available except for the Crinone require multiple doses per day or are messier leading to a discharge. The short half life of the natural progesterone dictates that multiple administrations are required to maintain normal levels in the luteal phase. The IM route has the advantage of continuous release of progesterone with the Depo form.

Multiple types of vaginal progesterone are FDA approved. The Vaginal gel (Crinone/Prochieve, Actavis Watson Pharmaceuticals, NJ, USA) contains 90 mg progesterone in 1.125 g of gel with a 2 % polycarbophil base and is approved once per day for supplementation and twice per day for replacement doses [24]. A second FDA-approved progesterone in a 100 mg progesterone tablet form is Endometrin, (Ferring Pharmaceuticals, NJ, USA) and is equivalent in efficacy to Crinone but needs to be given 2–3 times per day [25, 26]. Another frequently used micronized progesterone is Prometrium given 200 mg tid vaginal. This product is not FDA approved for this indication (Utrogestan, Ferring Pharmaceuticals, West Drayton, UK and Prometrium, Abbott Laboratories, Illinois, USA). Compounded 100 or 200 mg suppositories in petroleum jelly base have also been used in USA.

As previously stated, IM progesterone, given at 50–100 mg daily, is also used widely, but requires daily injections that are difficult to self administer and has lead to irritation and in some cases allergic responses and abscesses [27]. Vaginal progesterone gel (Crinone 8 %,

90 mg) has been shown to have equal efficacy with a daily dose and is less painful to administer, but subjects have complaints of clumping of the gel and discharge which can be decreased by application in the mornings. The literature on IVF cycles report that use Crinone once daily is as effective as IM progesterone in terms of endometrial development and results in similar pregnancy rates for supplemental IVF cycles. Twice daily dose is recommended in replacement cycles [27, 28]. The vaginal products on the market all have similar side effects of vaginal leakage, local irritation, discomfort with sexual intercourse, possible variability of drug absorption due to weight or vaginal epithelial thickness, and discharge.

Table 1 Rationale for progesterone vaginal ring

Advantages of vaginal ring
It permits the controlled release of the drug for long-term or short-term use
Less frequent dosing will be required avoiding daily or 2–3X daily administration
More convenient and reliable drug delivery is expected allowing low drug dose
Patient comfort and convenience are likely to be improved, and it does not interfere with coitus
Possible decrease in vaginal excretions and discharge
Because of the uterine first-pass effect, vaginal administration results in higher endometrial progesterone levels

Progesterone Vaginal Ring for Luteal support

The vaginal ring has the advantage of compliance. The vaginal ring that was produced by Barr Pharmaceuticals contains an active progesterone attached to a polymerous material that releases the drug slowly over a period of a week. The ring is inserted into the vaginal canal. The authors studied this novel and controlled release vaginal ring system used for progesterone replacement that is not yet FDA approved [23]. There is another vaginal ring produced in Europe, Prochieve, which provides continuous release of progesterone for up to 90 days. The ring releases 10 mg of progesterone daily, leading to plasma concentrations of 10–20 nmol/L (3.1–6.3 ng/mL). This dose was found to be the minimum necessary dose to advance the endometrium to the secretory phase. A RCT performed in South America compared the vaginal progesterone ring to intramuscular progesterone for use in both IVF and oocyte donation cycles. They report an increased, but not significant clinical pregnancy rate and statistically significant increased implantation rate with the vaginal ring (VR) [29]. The clinical pregnancy rates for the VR progesterone in the study by Zegers-Hochchild et al. were 36.6 and 39.8 % for fresh IVF and fresh oocyte donation, respectively. In the same study, the clinical pregnancy rates are reported as 36.6 and 28.6 % for the standard IM protocol for fresh IVF and fresh oocyte donation, respectively [29].

Another VR (Progering) is available for contraception. Progering is not yet available in the US. It is made of silicone with micronized progesterone releasing 10 mg progesterone per day. It lasts 3 months with slow sustained release with slowly decreasing but adequate concentrations over the 3 month period. Similar to other progesterone only contraceptives, irregular bleeding patterns are common.

Progesterone VR for either partial luteal support in non-donor IVF cycles or for complete luteal support in donor IVF cycles may be advantageous for a number of reasons summarized in Table 1.

A small pilot study conducted by our center compared weekly progesterone VR for luteal phase replacement in donor oocyte with the vaginal gel product (VG) [23]. In a "mock cycle," VR was able to adequately transform the endometrium, and when used during an actual embryo transfer cycle, pregnancy rates were similar to those achieved with the VG.

This progesterone VR is an investigational product made by Barr Pharmaceuticals, now part of Teva. It has been studied in clinical trials and was found to be effective, safe, and well tolerated [23, 30]. The product is made of silicone, which is known for low toxicity, good thermal stability, and easy diffusion of low molecular weight component like progesterone. Disadvantages may include manufacturing cost, high temperatures needed during processing, and the need to discard after use.

The Phase 3 RCT trial was recently published reporting 1,297 women undergoing fresh cycles of IVF, who were randomized 1:1 with VR changed weekly versus 8 %VG administered once daily [30]. The primary outcome of the study was to compare clinical pregnancy rates using progesterone supplementation with VR versus VG in women undergoing IVF followed by embryo transfer on cycle day three. Clinical pregnancy rates at 8 and 12 weeks gestation showed no differences between groups with excellent clinical pregnancy rates of 49.3 % at 8 weeks and 48.2 % at 12 weeks. These results are comparable with reported ART rates. Live birth rates and other pregnancy parameters were similar between the two groups. The weekly progesterone VR appeared to be well tolerated by the subjects without any issues with expulsion of the ring, irritation, or discharge, and safety was also established without any differences in AEs between groups.

Conclusion

Weekly progesterone VR is not currently FDA approved, but in studies it has been shown to be an effective and safe

alternative to other forms of vaginal progesterone for luteal supplementation in women undergoing IVF. A VR luteal support may be convenient and have fewer side effects. The women maintained the vaginal ring in for 1 week and were permitted to remove it up to 1 h at a time per day. There were no issues of expulsion of the ring or any difficulties with placement.

The ring was less messy than the vaginal gel. Further studies are needed in women older than 35 years of age as well as in the recipient population. Designing rings with different concentrations of continuous release may be more appropriate in the frozen and donor recipient cycles where complete replacement is needed. Aggressive luteal support protocols are being developed for such replacement cycles as well as cycles that employ a GnRH agonist trigger instead of an hCG trigger to induce ovulation.

Debate persists as to how the optimal serum progesterone levels relate to the local tissue levels and the superiority of intramuscular progesterone. There is also debate as to the optimal start time and duration of progesterone treatment during ART cycles, particularly if the cycle results in a pregnancy. In addition to safety and efficacy, there is a trend toward "gentler" IVF protocols in which patient comfort and convenience play an increasingly important role in selection of luteal progesterone modality. Large prospective clinical trials are needed to determine the ideal progesterone-based luteal phase protocol for ART replacement cycles.

Compliance with ethical requirements and Conflict of interest No source of funding and no disclosures. This review has not been submitted and is not under review by any other journal and has not been previously published. The authors have no conflicts of interest.

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