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REVIEW

Luteal phase support in assisted reproductive technology treatment: focus on Endometrin® (progesterone) vaginal insert

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Abstract: Supplementation of progesterone in the luteal phase and continuance of progesterone therapy during the first trimester has been found in several studies to have benefits in promoting fertility, preventing miscarriages and even preventing pre-term labor. Though it can be administered orally, intramuscularly or even sublingually, a very effective route with fewer side effects can be achieved by an intravaginal route. The first vaginal preparations were not made commercially but were compounded by pharmacies. This had the disadvantage of lack of control by the Food and Drug Administration (FDA) ensuring efficacy of the preparations. Furthermore there was a lack of precise dosing leading to batch to batch variation. The first commercially approved vaginal progesterone preparation in the United States was a vaginal gel which has proven very effective. The main side effect was accumulation of a buildup of the vaginal gel sometimes leading to irritation. Natural micronized progesterone for vaginal administration with the brand name of Utrogestan A® had been approved even before the gel in certain European countries. Endometrin® vaginal tablets are the newest natural progesterone approved by the FDA. Comparisons to the vaginal gel and to intramuscular progesterone have shown similar efficacy especially in studies following controlled ovarian hyperstimulation and oocyte egg retrieval and embryo transfer. Larger studies are needed to compare side effects.

Keywords: progesterone vaginal tablets, luteal phase, miscarriage, pregnancy rates

The importance of progesterone for health and fertility

Normal ovulating women secrete progesterone during the second half of the menstrual cycle by the corpus luteum which forms from the dominant follicle from which the oocyte has been released. Since the corpus luteum dominates this part of the cycle it is known as the luteal phase. Progesterone induces a secretory transformation of the uterine glands, increases vascularity of the endometrial lining, and stabilizes the endometrium in preparation for embryo implantation. Progesterone is also important in interacting with progesterone receptors on gamma/delta T cells leading to the expression of a protein that interferes with natural killer cells especially at the maternal fetal interphase.[1–3]

For those women not trying to conceive the absence or diminished secretion of progesterone may lead to endometrial hyperplasia or endometrial cancer or merely abnormal uterine bleeding. Treatment with synthetic progestins, eg, oral medroxyprogesterone acetate, will effectively provide protection. However, because of some fear linking this oral compound with breast cancer, some women may prefer natural progesterone.

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There are some women trying to conceive naturally who may fail to do so because of a deficiency in progesterone even in those women who appear to be ovulating.[4–6] Treatment with compounded vaginal suppositories has been found to greatly improve pregnancy rates in women who have a luteal phase defect despite having regular menses and attaining a mature follicle.[6,7] In fact, in women with out-of-phase endometrial biopsies the presence of "pure" luteal phase defects, in which the dominant follicle attains an 18–24 mm dimension associated with a serum estradiol >200 pg/mL, occurs in a majority of these women with regular menses.[6] In this circumstance vaginal progesterone suppositories were found to achieve superior pregnancy rates compared to the more commonly used follicle maturing drugs, eg, clomiphene citrate or gonadotropins.[6,8]

In addition, luteal phase and first trimester support with extra vaginal progesterone suppositories were found useful (at least by this author) to reduce miscarriage rates in the minority of women with regular menses and luteal phase deficiency who seem to require follicle maturing drugs and in completely anovulatory women requiring either clomiphene citrate or gonadotropins for follicular maturation.[6,9]

Vaginal progesterone suppositories have been demonstrated to lower miscarriage rates even in those women not taking follicle maturing drugs.[10,11] Some of its benefits in reducing miscarriage risk may be through the stimulation of immunomodulatory proteins that inhibit natural killer cell cytolytic activity and cause a shift from TH1 to TH2 cytokines.[12,13] The use of vaginal progesterone during the first trimester has even been associated with reducing the risk of preterm deliveries.[14]

Assisted reproductive technology and progesterone supplementation

The one area of assisted reproductive technology where there is no question about the need for supplemental progesterone is in women with ovarian failure who become donor oocyte recipients. These women need to achieve normal endometrial development through the artificial use of estrogen followed by progesterone.[15,16] Though one could transfer frozen-thawed embryos in the luteal phase of natural cycles or ovulatory cycles induced by follicle maturing drugs in women with normal ovarian function, most in vitro fertilization centers use the artificial estrogen progesterone regimen described for donor oocyte recipients for women having frozen embryo transfer(s).

When using controlled ovarian hyperstimulation (COH) for purposes of in vitro fertilization-embryo transfer (IVF-ET) most add supplemental progesterone in the luteal phase. Some do so because they believe that the use of gonadotropin releasing hormone agonists or antagonists used to prevent a premature LH surge may have adverse effects on corpus luteal function.[17,18] There are others who think that the adverse effect on luteal function is related to the high levels of serum estradiol and progesterone generated by multiple corpora lutea[19,20] Two meta-analyses of luteal phase support for IVF-ET cycles both found higher live delivery rates with supplement progesterone compared to placebo.[21,22] Progesterone seems to be as effective as supplemental hCG injection but with a much lower risk of the ovarian hyperstimulation syndrome.[21]

Various routes of administering natural progesterone

One way of administering progesterone is by intramuscular (IM) injection. It is rapidly absorbed and produces measurable serum levels within 2 to 8 hours. It has a slow clearance when administered in an oil vehicle.[23] However IM progesterone in oil can be associated with a lot of side effects. It is not unusual for women to develop an allergy to the peanut oil vehicle. Sometimes the progesterone is suspended then in olive oil and sometimes in ethyl oleate. However other complications including sterile abscesses, bleeding into the muscle and pain at the injection site have occurred. There have even been reported cases of acute eosinophilic pneumonia.[24,25] Furthermore the use of IM progesterone requires the aid of another person for administration.

Parenteral IM progesterone has been used for treating infertility and miscarriages for over 45 years.[4] Compounded progesterone vaginal suppositories have been used for over 20 years.[4,6,7,26–27] One of the disadvantages of vaginal progesterone suppositories compounded by pharmacies is that there is no control on batch to batch variations with no governing agency watching for quality control. Furthermore the suppositories result in a significant vaginal build up causing vaginal irritation.[28] They leak at room temperature and thus are messy and may lead to yeast infections.[28] One can reduce the irritation from these vaginal suppositories by adding vitamin E to the suppository.

In order to improve the efficacy and reduce side effects of vaginal progesterone there have been attempts at commercial development of vaginal progesterone. These US Food and Drug Administration (FDA) approved preparations will be discussed subsequently.

There has been commercial development of progesterone which can be administered orally. Oral progesterone in

100 and 200 mg tablets has been marketed under the brand same Prometrium® (Solvay Pharmaceuticals Inc., Marietta, GA, USA). However it is rendered mostly ineffective by the rapid metabolism that occurs by the rapid first pass effect in the liver.[29] Thus though the drug produces good serum levels of progesterone the concentration is not very high in the endometrium where it counts.[30] Thus oral progesterone is considered much less effective than IM or vaginal progesterone.[29,30] Furthermore the metabolites of oral progesterone can cause significant side effects such as lightheadedness, vertigo, drowsiness, and gastric discomfort.

Another oral progesterone that has been used in Europe for IVF-ET cycles is called dydrogesterone (Duphaston®; Solvay Pharmaceuticals, The Netherlands).[31] Its efficacy and side effects compared to Prometrium® are not known by this author because of his lack of experience with this particular drug.

Vaginal progesterone preparations approved by the FDA

Progesterone gel – Crinone®

Vaginal progesterone achieves lower serum levels but higher progesterone levels in the endometrial tissue than IM progesterone.[32,33] Crinone® (Columbia Laboratories Inc., Livingston, NJ, USA) vaginal gel was the first progesterone preparation in the US including oral or IM preparations approved for IVF-ET. It adheres very effectively to the vagina. Thus a 90 mg one time daily insertion may be equal to 400 to 600 mg compounded vaginal suppositories. This adhesiveness leads to one of the main side effects of Crinone® vaginal gel, which is an accumulation of a significant build-up of the vaginal gel leading sometimes to irritation.

FDA-approved vaginal progesterone tablets

The main purpose of this manuscript is to review all information available concerning the newest FDA approved vaginal progesterone Endometrin® vaginal tablets. To do so I did a Medline search from 2000 until November, 2008 and including searches of 10 journals dealing with reproductive endocrinology and infertility. Furthermore to include the latest information I included presentations from the 2008 American Society for Reproductive Medicine meeting which I attended.

Endometrin® (Ferring Pharmaceuticals, Parsippany, NJ, USA) vaginal tablets (100 mg) are the newest vaginal natural progesterone approved by the FDA. A theoretical advantage of Endometrin® compared to the vaginal suppository is that the tablets are made to absorb the vaginal secretions and disintegrate into an adhesive powder that adheres to the vaginal epithelium thus facilitating sustained absorption.[34] Theoretically the formulation would cause less perineal irritation.[34]

A study was performed comparing absorption and the side effects of perineal irritation from Endometrin® with those of a commercially available vaginal progesterone suppository available in Europe known as Cyclogest® (Shire Pharmaceuticals Ltd., UK). The study found that 200 mg of Endometrin® was able to produce the same serum levels after 6 days compared to 800 mg Cyclogest®.[33] Though there was no significant difference in vaginal irritation between the two preparations there was a trend for less irritation from Endometrin®.[33]

Efficacy of Endometrin®

The best test for efficacy of a progesterone preparation is to evaluate it under conditions where progesterone is critically required for the achievement of a pregnancy. One such circumstance is to prepare the endometrium for embryo transfer in women with absent or non-functioning ovaries using donor oocytes.[15,16,35] Adequate late luteal phase histologic changes were noted in women whose uteri were prepared with estrogen and Endometrin® as the type of progesterone.[36,37] The Endometrin® was as effective in causing the appropriate secretory changes as had been demonstrated for Crinone® and allowed higher serum levels of progesterone.[36,37] The aforementioned Endometrin® studies did not include pregnancy rates.[36,37]

Endeometrin® for luteal phase support in IVF-ET cycles

The efficacy of Endometrin® vaginal tablets used in the luteal phases following oocyte retrieval on pregnancy rates was compared to Crinone® vaginal gel 8% in a multicenter randomized prospective trial.[38] Clinical pregnancy rate with Endometrin® 100 mg 2 × daily was 40.6% (163/404) vs 45.3% for Endometrin® 3 × daily vs 43.1% (174/403) with Crinone vaginal gel 8% once daily. The comparable ongoing pregnancy rates were 38.5% (156/404) 42.5% (171/404), and 42.0% (170/403), respectively.[38]

A comparison of Endometrin® vaginal tablets with intramuscular progesterone in three studies that were the only ones by different research groups found in my search is shown in Table 1.[23,39,40] There was a significantly higher clinical pregnancy rate with IM progesterone versus Endometrin® vaginal tablets (42.6% vs 37.0%) ($p = 0.015$). Only the Khan et al[23] and Mitwally et al[39] studies provided miscarriage rates. There was no significant difference in ongoing pregnancy rates with IM progesterone (47.0%) vs Endometrin® (44.6%).

Table 1 Clinical and ongoing/delivered pregnancy rates following IVF-ET according to luteal phase support with Endometrin® vaginal tablets vs IM progesterone – a compilation of 3 studies

Study	Endometrin®			IM progesterone		
	No. of cycles	No. clin preg	No. ongoing delivered preg	No. of cycles	No. clin preg	No. ongoing delivered preg
Khan[23]	23	11 (47.8%)	11 (47.8%)	200	103 (51.5%)	94 (47.0%)
Mitwally[39]	145	71 (49%)	64 (44.1%)	399	210 (53%)	188 (47.1%)
[a]Beltsos[40]	568	191 (35.4%)		751	263 (35.1%)	
[b]Total clin preg	736	273 (37.0%)		1350	576 (42.6%)	
[d]Total ongoing preg	168		75 (44.6%)	599		282 (47.0%)

[a]Ongoing/delivered pregnancy rates not available.
[b]p = 0.015 Pearson chi-square analysis.
[c]p = NS Pearson chi-square analysis.

Summary and conclusions

Endometrin® seems to be an effective method of providing progesterone to the endometrium. It is superior to oral progesterone tablets in that it is more effective at the endometrial level with less side effects. It does not appear to be more effective than IM progesterone despite attaining a higher endometrial concentration in the endometrium. However it provides a lot fewer side effects. It is equally effective in achieving live deliveries compared with Crinone® vaginal gel. It is not clear if Endometrin® is less irritating than Crinone® but there may be less vaginal accumulation of by-product. Crinone® is more convenient however because of the need of only a single application. Endometrin® may be less irritating than compounded progesterone suppositories at least when the latter is not compounded with vitamin E. The use of Endometrin® avoids the possibility of batch to batch variation with progesterone concentration by compounding pharmacies but the compounded vaginal suppositories are generally significantly less expensive. At present there are multicenter prospective randomized IVF-ET trials using a novel progesterone ring in the luteal phase of IVF-ET cycle and the results are being compared with "controls" taking Crinone®. The progesterone ring may prove to be the best tolerated of all progesterone preparations and preliminary data suggest equal efficacy.

The intent of this manuscript was not to provide proof that progesterone therapy improves the chances of a live birth following IVF-ET or in other circumstances, eg, women with infertility, those requiring follicle stimulating drugs or those with a history of previous miscarriage. This author is one of the physicians who touts the benefits of progesterone.[41] However, the reader should be aware of some of the negative views expressed by Drs Malik and Regan.[42] This manuscript merely reviews the use of this new progesterone preparation and mentions some of its advantages over some of the other preparations. For those clinicians who believe in the benefits of progesterone supplementations in assisted reproductive technology, Endometrin® appears to be an efficacious preparation with equal efficacy to other vaginal preparations in achieving viable pregnancies, with certain advantages over other preparations.

Disclosures

The author declares no conflicts of interest.

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