

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

Jerome H Check

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Camden, New Jersey, USA

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.

Correspondence: Jerome H Check
7447 Old York Road, Melrose Park,
PA 19027
Tel +1 215 635 4156
Fax +1 215 635 2304
Email laurie@ccivf.com

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 name 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}

Endometrin[®] 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 al²³ and Mitwally et al³⁹ studies provided miscarriage rates. There was no significant difference in ongoing pregnancy rates with IM progesterone (47.0%) vs Endometrin[®] (44.6%).

Table I 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%) | |
| ^c Total ongoing preg | 168 | | 75 (44.6%) | 599 | | 282 (47.0%) |

^cOngoing/delivered pregnancy rates not available.

^bp = 0.015 Pearson chi-square analysis.

^ap = 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.

References

1. Szekeres-Bartho J, Barakonyi I, Polgar B, et al. The role of gamma/delta T cells in progesterone-mediated immunomodulation during pregnancy: a review. *Am J Reprod Immunol.* 1999;42:44–48.
2. Check JH, Szekeres-Bartho J, O'Shaughnessy A. Progesterone induced blocking factor seen in pregnancy lymphocytes soon after implantation. *Am J Reprod Immunol.* 1996;35:277–280.
3. Check JH, Arwitz M, Gross J, Szekeres-Bartho J, Wu CH. Evidence that the expression of progesterone-induced blocking factor by maternal T-lymphocytes is positively correlated with conception. *Am J Reprod Immunol.* 1997;38(1)6–8.
4. Jones GS, Poumand K. An evaluation of etiologic factors and therapy in 555 private patients with primary infertility. *Fertil Steril.* 1962;13:398–410.
5. Soules MR, Wiebe RH, Aksel S, et al. The diagnosis and therapy of luteal phase deficiency. *Fertil Steril.* 1977;28:1033–1037.
6. Check JH, Nowroozi K, Wu CH, Adelson HG, Lauer C. Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. *Int J Fertil.* 1988;33(4):252–256.
7. Check JH, Adelson HG. The efficacy of progesterone in achieving successful pregnancy: II, in women with pure luteal phase defects. *Int J Fertil.* 1987;32:139–141.
8. Check JH. Progesterone therapy versus follicle maturing drugs – possible opposite effects on embryo implantation. *Clin Exp Obst Gyn.* 2002;29:5–10.
9. Check JH, Chase JS, Adelson HG, Teichman M, Rankin A. The efficacy of progesterone in achieving successful pregnancy: I. Prophylactic use during luteal phase in anovulatory women. *Int J Fertil.* 1987;32:135–138.
10. Check JH, Chase JS, Nowroozi K, Wu CH, Adelson HG. Progesterone therapy to decrease first-trimester spontaneous abortions in previous aborters. *Int J Fertil.* 1987;32:192–193.
11. Check JH, Winkel CA, Check ML. Abortion rate in progesterone treated women presenting initially with low first trimester serum progesterone levels. *Am J Gynecol Health.* 1990;(2):63–64.

12. Szekeres-Bartho J, Faust Z, Varga P. The expression of a progesterone induced immunomodulatory protein in pregnancy lymphocytes. *Am J Reprod Immunol*. 1995;34:342–348.
13. Check JH, Ostrzenski A, Klimek R. Expression of an immunomodulatory protein known as progesterone induced blocking factor (PIBF) does not correlate with first trimester spontaneous abortions in progesterone supplemented women. *Am J Reprod Immunol*. 1997;37:330–334.
14. Check JH, Lee G, Epstein R, Vetter B. Increased rate of pre-term deliveries in untreated women with luteal phase deficiencies – a preliminary report. *Gynecol Obstet Invest*. 1992;33:183–184.
15. Lutjen P, Trounson A, Leeton J, et al. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature*. 1984;307:174–175.
16. Navot D, Laufer N, Kopolovic J, et al. Artificially induced cycles and establishment of pregnancies in the absence of ovaries. *N Engl J Med*. 1986;314:806–811.
17. Smitz J, Devroey P, Camus M, et al. The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT. *Hum Reprod*. 1988;3:585–590.
18. DiLuigi AJ, Nulsen JC. Effects of gonadotropin-releasing hormone agonists and antagonists on luteal function. *Curr Opin Obstet Gynecol*. 2007;19:258–265.
19. Fatemi HM, Camus M, Kolibianakis FM, et al. The luteal phase of recombinant follicle-stimulating hormone/gonadotropin-releasing hormone antagonist in vitro fertilization cycles during supplementation with progesterone or progesterone and estradiol. *Fertil Steril*. 2007;87:504–508.
20. Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. *Hum Reprod Update*. 2007;13:581–590.
21. Daya S, Gunby J. Luteal phase support in assisted reproduction cycles. *Cochrane Database Syst Rev*. 2004;CD004830.
22. Nosarka S, Kruger T, Siebert I, Grove D. Luteal phase support in in vitro fertilization: meta-analysis of randomized trials. *Gynecol Obstet Invest*. 2005;60:67–74.
23. Khan N, Richter KS, Newsome TL, Blaker EJ, Yankov VI. Matched-samples comparison of intramuscular versus vaginal progesterone for luteal phase support after in vitro fertilization and embryo transfer. *Fertil Steril*. 2008. [Epub ahead of print]
24. Bouckaert Y, Robert F, Englert Y, De Backer D, De Vuyst P, Delbaere A. Acute eosinophilic pneumonia associated with intramuscular administration of progesterone as luteal phase support after IVF: case report. *Hum Reprod*. 2004;19:1806–1810.
25. Veysman B, Vlahos I, Oshva L. Pneumonitis and eosinophilia after in vitro fertilization treatment. *Ann Emerg Med*. 2006;47:472–475.
26. Soules MR, Wiebe RH, Aksel S, et al: The diagnosis and therapy of luteal phase deficiency. *Fertil Steril*. 1977;28:1033–1037.
27. Wentz AC, Herbert CM, Maxson WS, et al. Outcome of progesterone treatment of luteal phase inadequacy. *Fertil Steril*. 1984;41:856–862.
28. Ng EH, Chan CC, Tang OS, Ho PC. A randomized comparison of side effects and patient convenience between Cyclogest suppositories and Endometrin tablets used for luteal phase support in IVF treatment. *Eur J Obstet Gynecol Reprod Biol*. 2007;131:182–188.
29. McAuley JW, Kroboth FJ, Kroboth PD. Oral administration of micronized progesterone: a review and more experience. *Pharmacotherapy*. 1996;16:453–457.
30. Licciardi FL, Kwiatkowski A, Noyes NL, Berkeley AS, Krey LL, Grifo JA. Oral versus intramuscular progesterone for in vitro fertilization: a prospective randomized study. *Fertil Steril*. 1999;71:614–618.
31. Belaisch-Allart J, Testart J, Fries N, Forman RG, Frydman R: The effect of dydrogesterone supplementation in an IVF programme. *Hum Reprod*. 1987;2:183–185.
32. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmouh L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. *Fertil Steril*. 1994;62:485–490.
33. de Ziegler D. Hormonal control of endometrial receptivity. *Hum Reprod*. 1995;10:4–7.
34. Levy T, Gurevitch S, Bar-Hava I, et al. Pharmacokinetics of natural progesterone administered in the form of a vaginal tablet. *Hum Reprod*. 1999;14:606–610.
35. Smitz J, Devroey P, Faguer B, et al. A prospective randomized comparison of intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement. *Hum Reprod*. 1992;7:168–175.
36. Pisov ALG, Fatum TM, Shufaro Y, et al. Simplified artificial endometrial preparation, using oral estradiol and novel vaginal progesterone tablets: a prospective randomized study. *Gynecol Endocrinol*. 2002;16:131–136.
37. Gibbons WE, Toner JP, Hamacher P, Kolm P. Experience with a novel vaginal progesterone preparation in a donor oocyte program. *Fertil Steril*. 1998;69:96–101.
38. Doody KJ, Schnell VL, Foulk RA, et al. Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. *Fertil Steril*. 2008. [Epub ahead of print].
39. Mitwally MF, Diamond MP, Abuzeld M. The vaginal micronized progesterone (Endometrin®) is as effective as intramuscular progesterone for luteal support in women undergoing IVF-ET. 64th Annual Meeting of the American Society for Reproductive Medicine, San Francisco, CA, November 8–12, 2008, abstract # P-761.
40. Beltsos A, Robinson A, Martin-Johnston MK, Lederer K, Sasada K, Byers M. Serum progesterone levels with endometrin compared to progesterone in oil and associated pregnancy outcomes in a large IVF center. 64th Annual Meeting of the American Society for Reproductive Medicine, San Francisco, CA, November 8–12, 2008, abstract #P-765.
41. Check JH. Debate for: Should progesterone supplements be used? Carp HJA Editor. In: *Recurrent pregnancy loss causes, controversies and treatment*. Informa Healthcare, 2007. p. 89–92.
42. Malik S, Regan L: Debate against: Should progesterone supplements be used? Carp HJA Editor. In: *Recurrent pregnancy loss causes, controversies and treatment*. Informa Healthcare; 0000. p. 93–96.

Therapeutics and Clinical Risk Management

Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS,

Submit your manuscript here: <http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal>

Dovepress

EMBASE, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.