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Editorial Article

An Editor's opinion of the recent committee opinion of the American Society for Reproductive Medicine that the luteal phase deficiency as a clinical entity causing infertility has not been proven

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Summary

Purpose: To present an opposing view to the recent conclusions reached by the Practice Committee of the American Society for Reproductive Medicine and a recent review of the role of progesterone in subfertility by Sonntag and Ludwig that there is no evidence to support using progesterone in the luteal phase as exclusive therapy. *Materials and Methods:* A large quasi randomized study not mentioned by either review is presented. *Results:* In this study published in 1989 when women with luteal phase deficiencies and subfertility were evaluated for follicular maturation, the majority seemed to form mature follicles. This majority group found far better with pregnancy outcome by taking exclusive progesterone in the luteal phase than follicle maturing drugs. A recent prospective series confirmed its beneficial effect. *Conclusions:* Physicians should not empirically treat with follicle maturing drugs but should use progesterone in the luteal phase, preferably in those women who seemingly create a mature follicle.

Key words: Luteal phase deficiencies; Progesterone; Follicle maturing drugs; Follicular maturation; Immunosuppression.

Introduction

As an Editor of this Journal, I was asked to write one editorial with each issue, especially, but not limited to my field of expertise and that is reproductive endocrinology and infertility. One editorial that I wrote was about the nature of the editorials that I would be writing entitled "The diagnosis and treatment of infertility – one person's philosophic approach" [1]. I reviewed in this editorial the difficulties encountered by the physician treating infertility in making therapeutic decision.

One physician recently was facetiously stated that it makes no sense to go to medical school because the insurance companies tell him what diagnostic tests he should perform, the drug representatives school him on what drugs he should use, and the patients have already self-diagnosed themselves by simply "going on line". The treating physician if not conducting there own review learn from lectures in their own hospitals or at national or international meetings by "experts" in the field and some predominantly base their treatment methods from didactic teaching and advice. Others will read the literature and will assume that the latest article from a reputable journal is the treatment philosophy to follow. Others rely heavily on committee practice opinions from the top experts in their field. The expectation is that the committee is composed of well-respected scientists in their field with both clinical and research experience. Ideally, each member should have both clinical and research experience, but a mixture of a team with clinical or research expertise would be acceptable. The committee chairman should do due diligence in selecting the appropriate committee members.

A recent practice committee of the prestigious American Society of Reproductive Medicine, published their opinion of the clinical relevance of luteal phase deficiency in the prestigious Journal Fertility and Sterility, in November 2012 [2]. The committee was composed of 19 well-known and well-published reproductive endocrinologists. I suspect, but am not sure that Samantha Pfeifer, M.D., was the committee chairman since she was listed first in the recognition of participants. The manuscript was received June 25, 2012 and was published online July 20, 2012. Thus it was not subject to peer review.

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There were five key points in their summary, but I will just quote two of them which is pertinent to my opinion about the committee views of use of luteal phase support with progesterone as a sole treatment entity for infertility. "No diagnostic test for luteal phase insufficiency has been proven reliable in a clinical setting. The roles of BBT, luteal progesterone levels, endometrial biopsy and other diagnostic studies have never been established and performance of these tests cannot be commended". I actually do not disagree with this statement and I have provided a detailed summary of what information has been accrued by these aforementioned studies and their limitations as a definitive test of luteal phase deficiency. Furthermore I mention the studies on putative molecular markers of endometrial development and their failure as a method to diagnose luteal phase deficiency [3]. In this article I mention that the hope will be in finding a correlation with luteal phase deficiency and insufficient generation of the immunosuppressive protein, the progesterone induced blocking factor (PIBF). Along with our fellow Rachael Cohen, I will be publishing another editorial in the near future concerning new and exciting findings concerning PIBF.

The second statement from the ASRM practice committee that I want to summarize is the following: "No treatment for luteal phase insufficiency has been shown to improve outcomes in natural, unstimulated cycles". There was no mention of any studies published by the members of this committee that showed that exclusive use of progesterone in the luteal phase was ineffective as a treatment modality for infertility. The committee states that "to date all attempts to link poor fertility endpoints have been unsuccessful" and they refer to four references [4-7]. However in my opinion, one cannot make the jump that because so far no good documentation of luteal phase deficiency exists that therefore treatment with progesterone is doomed for failure.

A lack of progesterone as a cause of infertility was first published in 1949 by Georgianna Jones who coined the term luteal phase deficiency [8]. In 1962 she published an uncontrolled series of 555 private patients and found that the use of progesterone in the luteal phase was associated with achieving pregnancies [9].

It is clear that once a pregnancy is established, surgically removing the ovary with the corpus luteum or the use of a progesterone receptor antagonist, e.g., mifepristone in the early first trimester will abrogate a pregnancy [10, 11]. However, another progesterone receptor antagonist, Ulipristal, which similar in structure and function to mifepristone, prevents binding of circulating progesterone to the progesterone receptor and inhibiting transcription and translation, documentation has been approved for emerging post-coital contraception [12]. The approval was granted upon the documentation that similar to other emerging contraceptives, e.g., levonorgestrel and combination estrogen-progesterone regimens, Ulipristal acetate also inhibits ovulation [13].

Ulipristal is more effective than levonorgestrel and other oral contraceptives emerging contraception and it is likely that the improved efficacy is related to inhibiting embryos from implanting if failure to prevent ovulation occurred [14]. There was no evidence of delayed endometrial maturation of the endometrium by a single dose of Ulipristal. However, there is a strong likelihood that this one time dosage, which has a half-life of 32 hours and can be detected seven days later, may have suppressed PIBF and thus allowed immune rejection of the conceptus [14-18]. Thus, the studies with Ulipristal in this manner suggest that inadequate progesterone effect, whether due to a small decrease in the integrated secretion of progesterone or relative resistance of the progesterone receptor to progesterone, may be present and may respond to therapy with extra progesterone and thus correct some infertility problem.

An integrated view on the diagnosis and treatment of luteal phase deficiency as a cause of subfertility was also recently published [19]. They wrote "Despite the existing recommendation for rational work-up in subfertility, luteal phase evaluation and progesterone therapy alone is still common in daily practice". I take this to mean that there is no rational reason for using exclusive luteal phase support with progesterone as a treatment for subfertility. Yet, in their review there is no mention of any studies refuting the use of exclusive progesterone therapy. The practice committee of the ASRM seem to favor the use of follicle maturing drugs in that they state that the "use of agents that induce ovulation may improve the fertility of subfertile women". Similarly, Sonntag and Ludwig state "as luteal deficiency is not an entity on its own but a consequence of defective follicular maturation and growth, it should be diagnosed and treated as such [19].

The use of follicle maturing drugs to correct luteal phase deficiency became popular in the late 1970's to early 1980's [20-22]. Sonntag and Ludwig implied that the empirical use of progesterone in the luteal phase may still be popular in Germany. However, in the United States, from evaluating thousands of subfertile couples, I would state that empirical usage of ovulation inducing drugs is the standard not only for reproductive endocrinologists, but OB/GYN generalists whereas exclusive luteal phase progesterone is uncommon.

Do I disagree that using follicle maturing drugs is never the right answer? No, sometimes they are appropriate. Do I agree that all cases of luteal phase deficiency should be treated with follicle maturing drugs? Absolutely not. Do I think that there is no use for exclusive use of progesterone in the luteal phase? No – I totally disagree and, in fact, would argue that more women should be treated with the exclusive use of progesterone than with drugs that induce ovulation. I will also state that I do not think that those women requiring follicle maturing drugs should be treated with them exclusively but in fact should also be supplemented with progesterone in the luteal phase.

To this point I have provided no better argument than the ASRM practice committee or Sonntag and Ludwig to favor my position but merely conjecture. However, in contrast to those opposed to progesterone, I have evaluated the efficacy of progesterone in the luteal phase as exclusive therapy. The study I refer to was published in a peer review journal in 1988 [23]. The study was a quasi-prospective randomized trial in that the randomization was by last digit of social security number rather than present day techniques as random numbers table and there was no placebo control [23]. The study randomly compared the use of clomiphene citrate (or human menopausal gonadotropins if the post-coital test was poor related to the anti-estrogen effect of clomiphene citrate) versus the exclusive use of progesterone vaginal suppositories in the luteal phase. The study group consisted of women with a minimum of one year of infertility with a male partner with normal semen parameters, bilateral tubal patency, and a normal post-coital test. After enrollment, if they showed evidence of an unruptured follicle in their initial evaluation of follicular maturation, they were excluded. Only women with endometrial biopsies performed in the late luteal phase which dated two or more days out-of-phase were included. One hundred consecutive women were randomly stratified into two groups based on their initial observation cycle - those who seemed to make a mature dominant follicle (using the aforementioned definition described earlier in this section), and those who showed follicle collapse and secretion of progesterone in the luteal phase, but did not seem to attain a mature follicle based on serial transvaginal sonography and serum estradiol levels. The 58 women making a mature follicle were randomized into treatment with clomiphene citrate or low dosage human menopausal gonadotropins in those with poor post-coital tests on clomiphene (n=27) or just with vaginal progesterone (n=31). The requirement was six cycles of good post-coital tests so the group receiving clomiphene had even extra cycles if in the first or subsequent cycles the post-coital test was poor when they would be switched to hMG. Only three of 27 (11.1%) conceived with follicle maturing drugs and two of three miscarried during the first six months of therapy. Thus the live delivery rate was only 3.7%. In contrast, 24 of 31 (77.4%) women conceived with luteal phase progesterone supplementation with only one miscarriage. The live delivery rate was 74.2% [24]. Interestingly, 25 women who failed to conceive during the six-month study with follicle maturing drugs during the first six months were switched to just progesterone in the luteal phase, and 16 of 25 (64.0%) conceived within six months with only one miscarriage [24]. In contrast, with a three-way randomization in the 42 women who did not attain a mature follicle, seven of ten conceived with follicle maturing drugs, but there were four miscarriages. Combining follicle maturing drugs in the follicular phase and progesterone in the luteal phase, the same percent achieved a pregnancy (14 of 20, 70%) but there was only one miscarriage. There were only three of 12 conceiving with just progesterone supplementation alone but no miscarriages [24].

If one did not separate the group according to follicle maturation, overall 43.8% achieved a clinical pregnancy with follicle maturing drugs *vs.* 60.4% with exclusive use of progesterone. The author is not aware of any subsequent study that refutes these data. Nevertheless, even to the present day, the authors having evaluated thousands of infertility couples and find a high percentage had been previously treated empirically with follicle maturing drugs by other infertility specialists or gynecologists successfully conceiving with progesterone.

As previously mentioned, the endometrial biopsy as performed in the aforementioned study has been criticized as to its accuracy in diagnosing luteal phase deficiency. This has led to a treatment philosophy in our infertility practice to empirically treat women with infertility with regular menses who seem to make mature follicles, have made partners with normal semen parameters, normal post-coital tests, and bilateral tubal patency with progesterone in the luteal phase. This is especially important in women aged 30 or above or even younger women with symptoms or signs of endometriosis. Though, as mentioned, there have been no studies refuting the aforementioned study published about 30 years ago, there have been no studies corroborating it either [24].

We decided to attempt to corroborate our previous study. However, with no remuneration, it would be difficult to convince women to be treated with a placebo for a period of time or give women follicle maturing drugs considering our previous negative data when using these drugs in the presence of mature follicles. Thus we decided to perform a prospective observational series of exclusive use of progesterone in the luteal phase without the use of an endometrial biopsy in women with a minimum of one year of infertility [3, 25].

For 32 women aged ≤ 39 with an average length of infertility of 2.3 years, (71.7%) achieved a live pregnancy past the first trimester within six months of progesterone therapy [3]. Also, of great importance, 26 of the 32 women had failed to have a successful pregnancy despite being previously treated for at least three cycles with follicle stimulation drugs prescribed by other previous physicians.

Clomiphene citrate and/or letrozole may cause vasomotor side effects, depression, thin endometria, ovarian cysts, hostile cervical mucus, and multiple follicles and thus multiple births. Gonadotropins, though not causing vasomotor symptoms, hostile mucus, or thin endometria, have an even greater likelihood of causing multiple births or persistent ovarian cysts (from unruptured follicles), but worst of all, they are extremely expensive. Based on these data, I would recommend empirical luteal phase progesterone therapy for infertility in women with "unexplained infertility" rather

than empirical use of follicle stimulating drugs, or worse, going to the most expensive of all therapies, in vitro fertilization. These data suggest that luteal phase deficiency is common but there is no good method at present to detect it. If the diagnosis is wrong, the treatment with progesterone is without risk and relatively inexpensive.

Perhaps computer searches from the ASRM Committee and Sonntag and Ludwig did not go back far enough to find this aforementioned 1988 study. However, these data were re-presented in the editorial I wrote in this journal in 2002 entitled "Progesterone therapy versus follicle maturing drugs – possible opposite effects on embryo implantation" [25]. They were also summarized in my editorial "Ovulation defects despite regular menses" [26]. These titles should not have been missed in any reasonable computer search, so my assumption is that these data were purposely left out of the article by the Practice Committee and Sonntag and Ludwig's article because the data conflicted with their personal opinions even though these opinions were unsubstantiated by any studies performed by these authors or others [2, 19].

Luigi Mastroianni, the head of reproductive endocrinology and infertility at the University of Pennsylvania School of Medicine was a pioneer in the field of infertility and he made a great number of discoveries that helped to allow the field of infertility to progress to its present state. I knew him well but he did not agree with my pro-progesterone attitude which was the Thomas Jefferson School of Medicine and later Robert Wood Johnson School of Medicine (Camden Division) philosophy. His students followed his doctrine and supplemental progesterone has not been a normal treatment modality at the University of Pennsylvania. I am assuming that the committee chair person would be the first member of the committee mentioned and Dr. Samantha Pfeifer is at this institution. The committee chair person enlists other members to form the committee and there are three additional members of the committee who were also once at the University of Pennsylvania. With 76 references in their article, I have to assume that the omission of our study was not fortuitous. Our data were not even mentioned to be criticized!

Prior to this editorial I wrote another editorial entitled "Infertility for the OB/GYN generalist" [27]. I mention our data in this article and I take the position that the generalist should consider empirical progesterone therapy themselves for women over 30 or those with pelvic pain for infertile women before referring to a reproductive endocrinologist because the "standard" of care by these specialist seem to be three cycles of intrauterine insemination with follicle maturing drugs (and frequently with no luteal phase support) then encouraging them to proceed to IVF. I emphasize in that editorial that the generalist can easily distinguish those with a potential luteal phase defect with immature follicles *vs.* mature follicles by evaluating serum estradiol at mid-cycle and looking for a level >200 pg/ml. This group will do very well with just progesterone support without risk or cost to the patient. This group is more common than those with follicle maturation defects. I can assure the reader that after 40 years of using luteal phase progesterone exclusively for selected cases I have not soured on this therapy one iota. I can also assure the reader that we have achieved many successful pregnancies by simply using progesterone support in the luteal phase in patients who have failed with ovulation drugs or even in vitro fertilization in patients who were previously treated by infertility specialists.

Thus, I return to my editorial which explained the type of editorials I will write for this Journal and re-emphasize the difficulty we all have in developing treatment paradigms for our patients [1]. The information leading practicing physicians to establish treatment protocols will be based on textbooks, publications in journals, lectures, review courses, and personal experience. Very rarely is there uniformity of opinions and thus the treating physician must decide what makes sense to them and base treatment on what they think is both logical and feasible [1]. There will be always biases. Though I have no commercial interests, my Ph.D. thesis was "The role of progesterone in promoting fertility and preventing miscarriage may be through the stimulation of immunomodulatory proteins". My basic science work coupled with clinical experience and publications could give me an edge against the members of the committee or Sonntag and Ludwig. However it could be considered that I am biased and will continue to try to put the square peg in a round hole.

I strongly suggest that whatever treatment course you choose based on what approach seems most logical and practical, you should keep statistics of your own patients so you can decide if this therapy seems efficacious or is it time to try an alternative therapy.

References

[1] Check J.H.: "The diagnosis and treatment of infertility. One person's philosophic approach". *Clin. Exp. Obstet. Gynecol.*, 2006, *33*, 69.
[2] The Practice Committee of the American Society for Reproductive Medicine: "The clinical relevance of luteal phase deficiency: a committee opinion". *Fertil. Steril.*, 2012, *98*, 1112.
[3] Check J.H., Cohen R.: "The role of progesterone and the progesterone receptor in human reproduction and cancer". *Exp. Rev. Endocrinol. Metab.*, 2013, *8*, 469.
[4] Bukulmez O., Arici A.: "Luteal phase deficiency: myth or reality". *Obstet. Gynecol. Clin. North Am.*, 2004, *31*, 727.
[5] Wentz A.C., Kossoy L.R., Parker R.A.: "The impact of luteal phase inadequacy in an infertile population". *Am. J. Obstet. Gynecol.*, 1990, *162*, 937.
[6] Kusuhara K.: "Clinical importance of endometrial histology and progesterone level assessment in luteal phase deficiency". *Hormone Res.*, 1992, *37*, 53.
[7] Balasch J,. Fabregues F., Creus M., Vanrell J.A.: "The usefulness of endometrial biopsy for luteal phase evaluation in infertility". *Hum. Reprod.*, 1992, *7*, 973.
[8] Jones G.S.: "Some newer aspects of management of infertility". *JAMA*, 1949, *141*, 1123.

[9] Jones G.S., Poumand K.: "An evaluation of etiologic factors and therapy in 555 private patients with primary infertility". *Fertil. Steril.*, 1962, *13*, 398.
[10] Cspo A.I., Pukkinen M.: "Indispensability of the human corpus luteum in the maintenance of early pregnancy: lutectomy evidence". *Obstet. Gynecol. Surv.*, 1978, *3*, 69.
[11] Herman W., Wyss R., Riondel A., Philbert D., Teutsch G., Sakiz E., Baulieu E.E.: "Effects of an anti-progestin steroid in women: interruption of the menstrual cycle or early pregnancy (author's transl)". *Contracept. Fertil. Sex. (Paris)*, 1982, *10*, 389. (Article in French)
[12] Snow S.E., Melillo S.N., Jarvis C.I.: "Ulipristal acetate for emergency contraception". *Ann. Pharmacother.*, 2011, *45*, 780.
[13] Brache V., Cochon L., Jesam C., Maldonado R., Salvatierra A.M., Levy D.P., *et al.*: Immediate pre-ovulatory administration of 30mg ulipristal acetate significantly delays follicular rupture. *Hum. Reprod.*, 2010, *25*, 2256.
[14] Keenan J.A.: "Ulipristal acetate: contraceptive or contragestive?" *Ann. Pharmacother.*, 2011, *45*, 813.
[15] Szekeres-Bartho J., Kilar F., Falkay G., Csernus V., Torok A., Pacsa A.S.: "Progesterone-treated lymphocytes of healthy pregnant women release a factor inhibiting cytotoxicity and prostaglandin synthesis". *Am. J. Reprod. Immunol. Microbiol.*, 1985, *9*, 15.
[16] Ivanova-Todorova E, Kyurkchiev DS, Nalbanski A, Timeva T, Shterev A, Kyurkchiev SD. Production and characterization of a novel monoclonal antibody against progesterone-induced blocking factor (PIBF). *J. Reprod. Immunol.*, 2008, *78*, 94.
[17] Cohen R., Check J.H., DiAntonio A., Srivastava M.D.: "Progesterone induced blocking factor (PIBF), an immunosuppressive protein that inhibits natural killer (NK) cell cytolytic activity, detected 3 days after embryo transfer (ET)". *Fertil. Steril.*, 2012, *98*, S28.
[18] Srivastava M.D., Thomas A., Srivastava B.I., Check J.H.: "Expression and modulation of progesterone induced blocking factor (PIBF) and innate immune factors in human leukemia cell lines by progesterone and mifepristone". *Leuk. Lymphoma*, 2007, *48*, 1610 .
[19] Sonntag B., Ludwig M.: "An integrated view on the luteal phase: diagnosis and treatment in subfertility". *Clin. Endocrinol.*, 2012, *77*, 500.
[20] Quagliarello J., Weiss G.: "Clomiphene citrate in the management of infertility associated with shortened luteal phases". *Fertil. Steril.*, 1979, *31*, 373.
[21] Hammond M.G., Talbert L.M.: "Clomiphene citrate therapy of infertile women with low luteal phase progesterone levels". *Obstet. Gynecol.*, 1982, *59*, 275.
[22] Downs KA, Gibson M.: "Clomiphene citrate therapy for luteal phase defect". *Fertil. Steril.*, 1983, *39*, 34.
[23] Check J.H., Nowroozi K., Wu C.H., Adelson H.G., Lauer C.: "Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects". *Int. J. Fertil.*, 1988, *33*, 252.
[24] Check J.H., Liss J., Check D.: "The beneficial effect of luteal phase support on pregnancy rates in women with unexplained infertility". *Fertil. Steril.*, 2013, *99*, S23.
[25] Check J.H.: "Progesterone therapy versus follicle maturing drugs - possible opposite effects on embryo implantation". *Clin. Exp. Obstet. Gynecol.*, 2002, *29*, 5.
[26] Check J.H.: "Ovulation defects despite regular menses: Part III". *Clin. Exp. Obstet. Gyncol.*, 2007, *34*, 133.
[27] Check J.H.: "A practical approach to diagnosing and treating infertility by the generalist in obstetrics and gynecology". *Clin. Exp. Obstet. Gynecol.*, 2015, *42*, 405.

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