Editorial Article

A practical approach to the prevention of miscarriage: Part 1 - progesterone therapy

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Summary

Purpose: To show evidence that progesterone therapy is useful in preventing miscarriages in women who are more prone to having them. *Methods:* Vaginal progesterone therapy was evaluated in women with a previous history of miscarriage or in women with infertility related to luteal phase defects. *Results:* The results favor the benefit of using progesterone to diminish the risk of miscarriage. Other methods of stimulating progesterone production, e.g., human chorionic injections, are also effective. *Conclusions:* Progesterone therapy, especially when given vaginally, is effective with few side-effects and is safe. Thus the evidence suggests that one should err on the side of over-treatment rather than under-treatment in certain circumstances, e.g., advanced woman's age, previous history of miscarriage, or the use of follicle maturing drugs.

Key words: Miscarriage; Luteal phase defects; Progesterone therapy; Human chorionic gonadotropin; Follicle maturing drugs.

Progesterone is essential for maintaining a normal pregnancy

Surgical removal of the ovary with the corpus luteum of pregnancy prior to eight weeks when there may not as yet be adequate placental progesterone production generally leads to a miscarriage [1]. The use of a progesterone receptor antagonist during the first trimester, e.g., mifepristone, leads to a high rate of spontaneous miscarriages [2-4]. In contrast high pregnancy rates can be achieved in anovulatory donor egg recipients without a corpus luteum by giving exogenous progesterone [5].

The luteal phase defect and endometrial biopsy

Over 55 years ago Noyes *et al*., stated and provided histologic dating of endometrial biopsies and provided daily characteristic changes of the endometrium throughout the luteal phase [6]. The out of phase endometrial biopsy (defined as endometrium taken from the mid to late luteal phase appearing two or more days earlier than expected) was first studied by Jones and Delfa and the conclusion they made over 55 years ago was that the luteal phase defect was estimated to be the apparent etiologic factor in 35% of first trimester miscarriages [7].

However, an infertility or recurrent miscarriage pathological state related to persistent defective corpus luteum function has become a debated issue over the years including the present time. It is not clear how the policy was established, maybe by an ad hoc committee, but the decision was made that to diagnose a luteal phase defect the biopsy must be either two or more than two (another debate) days out of phase in two consecutive cycles [8]. Thus by this definition only a woman with two consecutive out of phase endometrial biopsies should be treated with progesterone if they have had a problem with recurrent miscarriages.

Nonetheless consider the paradigm of a woman who has a luteal phase deficiency in 50% of her menstrual cycles. If progesterone therapy would reduce her risk of another miscarriage by 50% and if sticking to the requirement of only treating if the biopsy is abnormal in two consecutive cycles, then only 25% of the women who could benefit from progesterone therapy in this paradigm would be offered progesterone treatment.

The other problem with establishing whether a woman has a luteal phase defect is whether the biopsy is more accurate when performed in the late luteal phase to gain more accumulative effect of progesterone [9-11] or mid-luteal phase when implantation occurs [12-14]. Other controversies involve whether abnormal should be considered if the biopsy is greater or equal to two days out of phase [15, 16] or greater than two days out of phase [17, 18]. Other concerns are that the same slide is frequently dated differently by different pathologists. These and other problems have led the majority of infertility specialists to abandon this diagnostic tool for infertility purposes. As I will discuss below, though I am a strong advocate that the use of exogenous progesterone can reduce the risk of miscarriage, I no longer use the endometrial biopsy to determine who should receive this therapy.

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Candidates for progesterone therapy to prevent miscarriage

The frequency of miscarriages in the normal population has been estimated to be approximately 14% [19]. One study suggested that approximately a third of women who previously had a miscarriage will have another loss in their next pregnancy [20].

Some clinicians argue that since accidental meiosis errors are responsible for the majority of any given miscarriage, many will advise a woman who had a miscarriage but no chromosomal evaluation of the fetus that probably based on statistics this was a fetus with an aneuploidy and that she has no greater chance of this happening again than a woman who did not previously miscarry.

If progesterone therapy can prevent miscarriage (and evidence of its efficacy will be presented subsequently) my argument is what if it was not a chromosome issue but a progesterone deficiency? I raise the question – which is worse, treating a woman with progesterone who did not need it, although she has a subsequent successful delivery that could have been achieved without progesterone, or a woman who has a need for progesterone but does not take it and subsequently has a miscarriage because of not taking it.

As women reach advanced reproductive age (≥ age 40) there is a higher rate of miscarriages related both to an increased rate of aneuploidy and also to an increased need for progesterone. A miscarriage at any age is psychologically devastating so if a trisomy abnormality is documented in a 41-year-old woman's first pregnancy and miscarriage, I would still recommend the use of supplemental progesterone from the early luteal phase throughout the first trimester because irrespective of the cause of the first loss she is more prone to another loss from either a chromosome abnormality, which cannot be helped, or a relative progesterone deficiency, which can be helped.

Since many women who are merely more prone to miscarriage from a progesterone deficiency may still have a normal outcome if untreated it would take a very large study to show a significant improvement by progesterone therapy for women with only one or two previous losses, especially with some live deliveries thrown into the mix. This group is referred to as secondary aborters.

A study using supplemental vaginal progesterone suppositories started at a low dose of only 25 mg twice daily in the luteal phase then doubled with a positive pregnancy test and with further increases in dosage for bleeding or cramping resulted in a miscarriage rate of only 10% (10 of 100) in women who had at least one previous miscarriage [21]. Breaking them down according to how many previous miscarriages they had, there was a 5% miscarriage rate (1 of 20) in those with one previous loss, 4.8% with two miscarriages (3 of 62) and 33% (6 of 18) with three or more losses. Interestingly all six women with three or more losses who miscarried despite progesterone therapy were successful in the second treatment cycle of progesterone therapy [21]. This was not a controlled study but the 10% miscarriage rate showed a trend to be lower than the normal expected miscarriage rate of 14% [19] and certainly less than the 33.3% rate found in women with previous losses [20].

A study by Yeko *et al*. found that when a pregnant woman had a serum progesterone level less than 15 ng/ml a miscarriage is inevitable [22]. However another study found that with aggressive progesterone therapy given at the point of a serum progesterone < 15 ng/ml that 70% of the women will proceed to have a successful live delivery [23]. Another study even found a 60% live delivery rate with a serum progesterone less than 8 ng/ml with the use of aggressive progesterone supplementation [24]. Thus other candidates for progesterone therapy to try to prevent miscarriage are women who present with low serum progesterone levels during there pregnancy [23, 24].

It is not clear what the proper level of progesterone is during pregnancy but most normal pregnancies in my experience have levels over 30 ng/ml three weeks after conception. Thus I would start a pregnant woman on progesterone supplementation if she presents with a level < 30 ng/ml and I would suggest raising the dosage if she was already on it.

Though a low serum progesterone level during pregnancy would prompt the decision to raise or initiate progesterone therapy, a normal serum progesterone level does not preclude the use of progesterone to prevent miscarriage. The main mechanism by which progesterone prevents miscarriage may be through the stimulation of immunomodulatory proteins that in turn inhibit natural killer cells from attacking the fetal semi-allograft [25-27]. The relative role of progesterone and lymphocyte immunotherapy will be discussed more fully in part II of this editorial. Suffice it to say now that this 34 kDa protein has been synthesized by recombinant DNA technology. The development of ELISA assays that allow rapid results will soon be available.

Obviously if I think that progesterone therapy benefits women even with a history of one previous miscarriage even when live births have occurred I would think it should benefit women with recurrent miscarriages defined as at least three consecutive miscarriages. Studies have shown that the risk of subsequent miscarriage in women with three to five consecutive miscarriages ranged between 42-86%, 41-72% and 23-51%, respectively [28-31]. A group of women with recurrent miscarriages with four previous losses experienced a 51% miscarriage rate in their next pregnancy supplemented with progesterone [32]. As will be discussed in part II this may be the group who will show a more impressive response with lymphocyte immunotherapy [32]. It should be noted that many of these women in the aforementioned study had progesterone therapy previously and still had a miscarriage [32]. Perhaps the miscarriage rate would be lower in women with ≥ 4 recurrent miscarriages who never previously had progesterone therapy who are now treated with the progesterone hormone for the first time.

Methods of administering progesterone

One way of administering progesterone is by intramuscular (IM) injection. It is rapidly absorbed and produces measurable serum levels within two to eight hours. It has a slow clearance when administered in an oil vehicle. 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 then suspended 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. Furthermore the use of IM progesterone requires the aid of another person for administration.

Parenteral IM progesterone has been used to treat infertility and miscarriages for over 45 years [7]. Compounded progesterone vaginal suppositories have been used for over 20 years [18, 33-36]. 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 [37]. They leak at room temperature and thus are messy and may lead to yeast infections [37]. One can reduce the irritation from these vaginal suppositories by adding vitamin E to the suppository.

To improve the efficacy and reduce side-effects of vaginal progesterone there have been attempts at commercial development of vaginal progesterone. These 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®. However it is rendered mostly ineffective by the rapid metabolism that occurs by the rapid first pass effect in the liver [38]. Thus though the drug produces good serum levels of progesterone the concentration is not very high in the endometrium where it counts [38]. Therefore oral progesterone is considered much less effective than IM or vaginal progesterone [39]. Furthermore the metabolites of oral progesterone can cause significant side-effects such as lightheadedness, vertigo, drowsiness, and gastric discomfort.

Vaginal progesterone preparation approved by the Food and Drug Administration

Progesterone gels - Crinone® and Prochieve®

Vaginal progesterone achieves lower serum levels but higher progesterone levels in the endometrial tissue than IM progesterone [40]. Crinone vaginal gel was the first progesterone preparation 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 a 400-600 mg compounded vaginal suppository. This adhesiveness leads to one of the main side-effects of Crinone vaginal gel and that is an accumulation of a significant buildup of the vaginal gel leading sometimes to irritation.

FDA approved vaginal progesterone tablets

Endometrin vaginal tablets (100 mg) are the newest vaginal natural progesterone approved by the FDA. The theoretical advantage of Endometrin compared to the vaginal suppository is that the tablets are made to absorb vaginal secretions and disintegrate into an adhesive powder that adheres to the vaginal epithelium thus facilitating sustained absorption [41]. Theoretically the formulation would cause less perineal irritation [41].

A study was performed comparing absorption and the side-effects of perineal irritation from Endometrin vs a commercially available vaginal progesterone suppository available in Europe known as Cyclogest [42]. The study found that 200 mg of Endometrin was able to produce the same serum levels after six days compared to 800 mg Cyclogest [42]. Though there was no significant difference in vaginal irritation between the two preparations there was a trend for less irritation from Endometrin [42].

Safety of progesterone treatment during pregnancy

The Food and Drug Administration (FDA) issued a warning stating that the use of synthetic progesterone or natural progesterone may be associated with various congenital abnormalities including VACTERL syndrome neural tube defects and heart abnormalities [8]. However, subsequent studies did not corroborate the FDA's warning finding no risk of birth defects with the use of supplemental progesterone during the first trimester [43, 44]. Despite the widespread use of supplemental progesterone with assisted reproductive technology the FDA has never rescinded the warning even though their own Obstetrics and Gynecology Advisory Board recommended not to put this label on the progesterone [8]. In fact the use of progesterone may prevent neonatal consequences by preventing preterm deliveries [45]. Nevertheless most manufactured items still are using the FDA's warning about progesterone.

Other therapies for luteal phase defects

As mentioned it is not my belief that only women with luteal phase defects may require progesterone therapy to prevent a miscarriage. Indeed in some instances the corpus luteum of pregnancy, which may have produced adequate hormones during the luteal phase, fails before the placenta is adequately secreting progesterone.

However, it is my contention that all women who have a luteal phase defect should be treated with extra proges-

terone. In a study of 100 consecutive women with a minimum of one year of infertility attributed to luteal phase defects as determined by endometrial biopsy the patients were divided into two groups according to whether they attained a mature follicle or not (as defined as reaching an average diameter of 18 mm and a serum estradiol ≥ 200 pg/ml) [34]. The group with mature follicles (n = 58) were either treated with follicle maturing drugs (n = 27) or supplemental vaginal progesterone (n = 31) [34]. Not only did only three of the 27 treated with follicle maturing drugs conceive within six months but two of the three had miscarriages. In contrast there were 24 of 31 conceiving in the 6-month period with supplemental progesterone with only one of the 24 having a miscarriage [34]. There were 25 women failing to conceive in the first six months with follicle maturing drugs treated with exclusive progesterone during the next six months; 16 conceived with only one miscarriage [34].

For the women with luteal phase defects and immature follicles seven of ten conceived but four of seven had a miscarriage. However in 20 women treated with the combination of follicle maturing drugs in the follicular phase and progesterone in the luteal phase 14 conceived with only one miscarriage [34]. Though only three of 12 with immature follicles conceived with just progesterone therapy, none of them miscarried [34]. Thus this study supported previous conclusions that supplemental progesterone therapy should be given even when follicle maturing drugs are not merely used in anovulatory women but in those with a luteal phase defects related to releasing the egg from an immature follicle [35].

There is evidence that anovulatory women with ovulation induction by follicle maturing drugs may still have persistent luteal phase defects in 30-50% of the cases [46, 47]. A matched controlled study found a 28% miscarriage rate in women treated with follicle maturing drugs without progesterone in the luteal phase vs only 6% of 50 women treated with both [21]. Thus in my opinion women with infertility related to anovulation or luteal phase defects related to releasing the egg before the follicle is mature should take progesterone in the luteal phase to decrease the risk of miscarriage [21, 34, 48].

The duration and amount of estradiol exposure during the follicular phase helps to develop endometrial progesterone receptors. Thus it is logical to not only treat women with a history of miscarriage with supplemental progesterone in the luteal phase but also the follicular phase should be corrected if an adequate serum estradiol is not attained.

It is the human chorionic gonadotropin made by the early pregnancy that is responsible for keeping the corpus luteum functioning during pregnancy. There is evidence that supplemental hCG during the luteal phase and first trimester can also reduce miscarriage rates [49-53]. A meta-analysis concluded that the use of hCG is beneficial in preventing miscarriage [54]. However it does not seem more beneficial than progesterone [55]. Disadvantages of hCG other than the injections is the risk of ovarian hyperstimulation in those women using higher dosages of follicle maturing drugs and the possibility of not being able to rescue a failing corpus luteum.

The corpus luteum not only makes progesterone but it also makes estradiol. Several studies have found low serum E2 levels in women who are aborting [56-59]. However, it is not clear if the low serum E2 is merely a marker for progesterone deficiency or if a low level plays a role in miscarriage. A study was performed evaluating E2 levels in women who miscarried vs women who did not who were adequately supplemented with progesterone [59]. The study did find much lower serum E2 levels in those who miscarried vs those who did not [59]. However there are no studies to my knowledge evaluating the effect of adding estradiol to progesterone therapy to decrease miscarriage risk.

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