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Editorial Article

Pros and cons of the use of progesterone to reduce miscarriage rates

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Summary

Purpose: To present flaws in the experimental design of a recent randomized controlled trial (RCT) published in the prestigious journal The New England Journal of Medicine (NEJM) concerning the lack of benefit of using progesterone (P) to prevent miscarriage. *Materials and Methods:* The RCT started vaginal P not until confirmation of pregnancy up to six weeks gestation. *Results:* Evidence is provided why a properly designed RCT should initiate P therapy in the early luteal phase to maximally inhibit the increase in cytotoxic leukocytes [especially natural killer (NK) cells] that are in the area of the site of implantation that are needed for uterine remodeling. The cytotoxicity of these cellular immune cells need to be suppressed or they may attack the fetal semi-allograft. Evidence is provided to support the hypothesis that the main effect of P is to stimulate the rise of an immunosuppressive protein called the P-induced blocking factor (PIBF). *Conclusions:* The RCT published in a late 2015 edition of the NEJM should not be regarded as a conclusive study showing no benefit of P in reducing risk of miscarriage. This is not only because of not starting the P in the early luteal phase, but also the type of P used. Some studies have found that vaginal P does not raise the PIBF levels nearly as well as intramuscular P.

Key words: Recurrent miscarriage; Vaginal progesterone; Intramuscular progesterone; Progesterone induced blocking factor; Immune rejection.

Introduction

As an Editor-in-Chief of this journal, one of my happy responsibilities is to write frequent Editorials. My first Editorial in 2006 was entitled "The diagnosis and treatment of infertility. One person's philosophic approach" [1]. In retrospect based on the subject matter of the multitude of editorials that I have written for the journal, I wish I had included miscarriage, and reproductive and gynecologic disorders in the title.

In that first issue I cautioned the reader that these editorials will be somewhat biased based on clinical experience and personal research. However, I would always present all sides of an argument. I mentioned how difficult it is for a physician to decide on a given treatment regimen even based on well performed properly conducted research studies. Unfortunately sometimes the truths of today are sometimes tomorrow's fallacies.

There are some physicians who are unwilling to treat a patient with a specific therapy unless there is a RCT trial that documents its efficacy and safety. Since sometimes different RCT studies on the same therapy reach different conclusions, sometimes one needs a referee which is a meta-analysis of RCT studies.

Many physicians will heed the conclusions of a properly designed RCT trial that is sufficiently powered, especially a multi-centered study. Such a study could change the method of treatment by a given physician that was previously based on the conclusions of a meta-analysis, of RCT trials if the new study, if added to the other ones used for the previous meta-analysis would shift the conclusions from effective to non-effective. Such a study could carry even more weight if published in a highly prestigious journal.

In our five part series on "A practical approach to the prevention of miscarriage" part one was on progesterone (P) therapy which was published in 2009 [2]. Our view on the efficacy of P in preventing miscarriage was based on both theory and our own studies touting its efficacy [2].

A Cochrane Database Systemic Review was published in 2013 [3]. In their meta-analysis they excluded 18 studies that evaluated the use of P or progestogens to prevent miscarriage that did not meet the strict criteria of their inclusion criteria [3]. Four of the 18 studies excluded were four of our studies that suggested a clear benefit of using P to decrease miscarriage rates that had been included in our aforementioned editorial [2, 4-6].

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The meta-analysis evaluated 14 trials including 2,158 women [3]. Overall the study found that regardless of gravidity and number of previous miscarriages, there was no statistical difference in the risk of miscarriage between progestogen, placebo, or no treatment groups [3]. However in a subgroup analysis of four trials involving women who had recurrent miscarriages (three or more consecutive miscarriages including 275 women] progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment. No statistically significant differences were found between the route of administration of progestogen (oral, intramuscular, vaginal] *vs*. placebo or no treatment [3].

One of the four studies by Goldzieher in 1964 used medroxyprogesterone acetate. The results of this properly randomized but very small study did not conclude that there was a significant difference in pregnancy rates with treatment group (2 of 14, 14%) miscarriage rate *vs.* placebo (5 of 18, 28%). One could state that the progestogen cut the miscarriage rate in half though it was way too underpowered to make the conclusion. The author does not state when the medroxyprogesterone acetate was started [7]. In one of the other studies by Swyer *et al.* in 1,953 P pellets were started no sooner than when the pregnancy was diagnosed and no later than the 10th week of gestation [8]. The study by Goldzieher was published in 1964 [7]. The most recent study of the four used in the sub-analysis by El-Zibdah was published in 2005, and it is important to note the progestogen used was oral dydrogesterone [9].

Thus, though I would like to use the recent meta-analysis to support my conclusion that the proper use of P can reduce the risk of miscarriages, despite the fact that these four studies met the inclusion criteria of the Haas and Ramsey, there are a lot of flaws in my opinion. Thus, I would not really use the recent meta-analysis to support my view of the positive benefit of P in preventing miscarriage [2].

In the book "Recurrent Pregnancy Loss: Causes, Controversies, and Treatment", the sections on controversies organizes the section with one invited author to present the pros of using a P supplementation to prevent miscarriage [10]. The con section was authored by Professor Leslie Regan [11]. A recent edition of this book will be available to the public and I authored again the section in the "pro" opinion of using P support and Professor Regan co-authored again the "con" section. Professors Rai and Regan were most likely invited to write the con section of the earlier publication and the recent one because of their publication in Lancet in 2006 entitled "Recurrent miscarriage which gave a negative view of the benefits of P supplementation [12].

Professors Regan and Rai are co-authors of a publication in an extremely prestigious journal (The New England Journal of Medicine) that is entitled "A randomized trial of progesterone in women with recurrent miscarriage" [13]. This study has the distinct advantage of being a highly proper RCT in that it was multi-centered, double-blinded, placebo controlled, and sufficiently powered [13]. The live birth rate was 65.8% (262 of 398) in the P treated women *vs*. 63.3% (271 of 428) for placebo [13]. There were 35 authors in this study!!

So, am I finally willing to concede the debate to Drs. Regan and Rai that P therapy in the first trimester does not improve the chance of a live birth in women with a previous history of recurrent pregnancy loss? Absolutely not!! What good is a very properly randomized multi-centered study with adequate power if it has a poor experimental design? In the remainder of this editorial I will present my argument about improper design.

From conception to the arrival of the blastocyst increased activity of the cellular immune system in the endometrium is needed to cause remodeling of the endometrium to prepare for implantation [14-19]. One of the main roles of P may be to negate the rejection of the fetal semi-allograft by these cellular immune cells that are present related to remodeling [20]. Evidence has been presented to support the hypothesis that one of the ways that P helps to suppress immune rejection of the early conceptus may be by the production of a 34-36 kDa splice variant from a parent centrosomal associated 90 kDa protein called the P-induced blocking factor (PIBF) [20]. Not only does the intracytoplasmic PIBF level rise with P exposure, but there is also a precipitous rise in the serum level even without exposure to the fetal semi-allograft [21, 22]. For these reasons, my contention is that if there is a critical time to supplement P to prevent miscarriage, it would be immediately after ovulation throughout the luteal phase. In the recent RCT from the New England Journal of Medicine "vaginal suppositories containing either 400 mg of micronized progesterone or matched placebo from a time soon after a positive urinary pregnancy test and no later than 6 weeks of gestation" was given [13]. Not starting the P in the luteal phase is a very serious flaw design in the study, and thus is the basis for my contention that the experimental design was poor.

The positive studies that we published that showed a positive benefit for P in preventing miscarriage used P starting in the early luteal phase [4-7]. However, they were not randomized to the satisfaction of Haas and Ramsey to be included in their meta-analysis, and thus would not meet the satisfaction of Professors Rai and Regan to influence P as a therapy for recurrent miscarriage, and probably some others who will not initiate a treatment, unless its benefit has been established by a properly designed, properly randomized prospective study which would be enhanced by it being multi-centered and sufficiently powered. Unfortunately, there have been ten years between the last adequate RCT by El-Zibdeh and the 2015 one from Coomarasamy *et al.* [9, 13]. The authors do concede in their discussion that their "study cannot address whether P supplementation could be more effective in reducing the risk of miscarriage if administered during the luteal phase of the cycle, before

confirmation of pregnancy" [13]. However, they did not mention any intention of repeating their study with the proper design, i.e., luteal phase use of P [13].

The recent RCT by Coomarasamy *et al.* and the Cochrane meta-analysis do support previous conclusions that P does not cause a risk to the fetus [3, 13, 23]. So supposing a couple seeks help for recurrent miscarriage. What therapy has been proven by properly designed RCT trials that would have a significant chance of reducing their risk of another miscarriage? If not P, I am not aware of any such treatment. So suppose ten years from now a properly designed RCT finally confirms the benefit of P therapy. Would the consulting specialist who insisted on the RCT study before therapy, and thus prescribed careful vigilance and benign neglect, have some regrets about not providing P therapy for their previous consulting couples? Or should they call the 35-year-old woman who consulted them before with the good news that at age 45 we can now try P to reduce the risk of miscarriage?

If a properly designed RCT study of luteal phase and first trimester use of P to prevent miscarriage is initiated, the proper type of P should be used. One study found no differences in any molecular marker in the luteal phase as long as a level of P of 5 ng/mL is achieved [24]. Thus, since the leading hypothesis is that if P does decrease miscarriage rates it most likely is by reducing the risk of immune rejection, especially by increasing intracellular and/or serum levels of PIBF [20], a properly designed study evaluating the efficacy of P should start therapy in the early luteal phase to decrease miscarriage rates and should use a type of P that raises PIBF levels.

It has been demonstrated that dydrogesterone, 17-hydroxyprogesterone, and 19-nortestosterone derivative progestogens do not raise PIBF at all [22]. Though vaginal P does raise serum PIBF it pails in comparison to intramuscular P or oral micronized P [22]. Unfortunately oral micronized P is metabolized through first pass through the liver [20]. Vaginal P does advance the secretory changes of the endometrium comparable to IM P. Thus my suggestion for a RCT is to either use IM P, or the combination of vaginal and oral micronized P. Thus, the Coomarasamy *et al* .study may not even be sufficient to at least conclude that taking P after the diagnosis of pregnancy is not sufficient to reduce miscarriage risk in women with a history of miscarriage since vaginal P may not be the right route of administration [13]. There are, in fact, data showing that in some circumstances taking P after a pregnancy has been confirmed can reduce risk of miscarriage. Yeko *et al.* found that 17 of 18 women with intrauterine pregnancies and serum P < 15 ng/mL had a miscarriage [25]. However, we demonstrated a miscarriage rate of only 30% when pregnant women were aggressively treated with a combination of IM and vaginal P [26]. In fact even with serum P level < 8 ng/mL, aggressive P therapy reduced the miscarriage rate to 40% [27].

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