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Review Article

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The Role of Membrane Progesterone Receptor Associated Proteins in Gynecological and Reproductive Disorders, And Cancers: An Editor's Historical Perspective

Part 2: Clinical benefits of P supplementation post-ovulation

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ABSTRACT

There is evidence that the development of spiral arteries from early luteal phase to the end of pregnancy are predominately formed not from neovascularization but through autoimmune stripping off of the thick walls on uterine arteries. These spiral arteries require a cell wall only 1 cell thick to allow nutrient exchange between mother and fetus. The invasion of cellular immune cells with 70% natural killer (NK) cells is facilitated by the effect of progesterone (P) in blocking dopamine to allow increased cellular permeability allowing infusion of irritants into pelvic tissue causing an inflammatory effect. These cellular immune cells do permeate the fetal placental microenvironment. Thus, they need to be subsequently suppressed, or they will attack the fetal semi-allograft. One mechanism used to suppress these NK cells, macrophages, and cytotoxic T-cells is by P activating membrane progesterone receptors (mPRs) to make certain immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) which, in turn, will abrogate the killing action of these cellular immune cells. Thus, supplementing the luteal phase with extra P may correct infertility, and prevent recurrent miscarriage, or preterm delivery. Sometimes if adding P is insufficient to fully negate the killing action of these cellular immune cells, one could treat the patient with a dopamine agonist to try to reduce excessive permeability leading to excessive inflammation.

Keywords: Immunomodulatory Proteins, Membrane Progesterone Receptor, Progesterone Induced Blocking Factor, Infertility, Miscarriage, Pre-Term Delivery, Progesterone

Potential Clinical Utility for Procreation Based on These Studies of the Mpr and Its Role in Making Pibf

The concept that insufficient secretion of P by the corpus luteum can be a cause of infertility dates back to seventy-five years ago [1]. The method to diagnose a lack of P by the corpus luteum (called a luteal phase defect) was by showing that histologic changes in the endometrium obtained by endometrial biopsy in mid luteal phase to 10 days after ovulation was abnormal (out of phase) if it showed the histologic pattern of more than 2 days earlier than it should be [2].

We performed an unpublished study about 40 years ago in which we found that most fertile women achieved a dominant follicle of 18-24mm with a serum estradiol (E2) over 200 pg/ml. About 35 years ago we published a manuscript that determined the frequency of achieving mature dominant follicles in women with a minimum of 1 year of infertility who had regular menses, patent fallopian tubes, and a normal post coital test 8-10 hours after intercourse, whose male partner had normal semen parameters, but where the female partner had an out of phase endometrial biopsy [3]. We determined that 58 of 100 women seemed to attain a mature follicle based on ultrasound and serum E2 criteria.

For the 58 women with mature dominant follicles, we randomly assigned them to using vaginal P supplementation in the luteal phase vs a follicle maturing drug (more often clomiphene citrate, but sometimes human menopausal gonadotropins). They were treated for 6 months unless a pregnancy ensued before that time. In 31 women treated exclusively with vaginal P, 24 of 31 conceived (77.4%) with only 1 miscarriage resulting in a live delivered pregnancy rate (LDPR) for 6 months of 74.2%.

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In contrast, for the 27 women randomized to follicle maturing drugs only (clomiphene or human menopausal gonadotropins) only 3 of 27 conceived (11.1%) and 2 had a miscarriage (6 months LDPR of only 3.3%) [3].

There was a 3-way randomization for women who did not attain a mature dominant follicle. Twelve women received exclusive vaginal P in the luteal phase but only 3 conceived with no miscarriages (clinical and LDPR of 25%). Ten received follicle maturing drugs only and seven conceived (70%) but 4 had a miscarriage resulting in a LDPR of only 30%. There were 20 patients who took a follicle maturing drug plus P in the luteal phase resulting in a clinical PR per transfer of 70% (14 of 20) (the same as follicle maturing drugs without supplemental P). However, instead of a 57.1% miscarriage rate there was only 1 of 14 who had a miscarriage (7%) and the LDPR per 6 months was 65% (13/20) [3].

Though it appeared that all other potential infertility factors were normal, nevertheless, there was the chance of a fortuitous, biased selection of patients in the mature dominant follicle group taking follicle maturing drugs only. However, 25 failures in that group subsequently were treated exclusively with P in the luteal phase during the next 6 months and 16 of 25 conceived in 6 months (64.0%) with only 1 miscarriage (6.3%) and a LDPR per 6 months of 60.0% [3].

The authors' interpretation of these data was as follows: 1) for women whose only apparent infertility factor is an out of phase endometrial biopsy, a slight majority make a mature dominant follicle vs releasing the egg before achieving an adequate serum E2 level. 2) P given in the luteal phase is far more effective to treat infertility than follicle maturing drugs without P supplementation in women who appear to make a mature dominant follicle but have an out of phase endometrial biopsy. 3) Though in women not attaining a mature dominant follicle despite regular menses additional P in the luteal phase besides the follicle maturation drug does not seem to increase the clinical PR compared to women taking follicle maturing drugs only, it seems to reduce the miscarriage rate. The study was not designed to answer the question as to whether using follicle maturing drugs and supplemental P in the luteal phase in women making mature follicles would increase, decrease, or not effect the LDPRs compared to P only [3].

There was always the possibility that despite attaining a mature follicle by the definition that fits most fertile women, that some women may need slightly more follicular maturation to achieve a good metaphase II egg and adequate mitochondrial DNA, or may need a slightly higher serum E2 to develop adequate induction of P receptors (either nPRs or mPRs). Theoretically, the anti-estrogen effect of clomiphene x 5 days could inhibit the development of PRs. Thus, a boost with gonadotropins in the late follicular phase would logically be a better choice than anti-estrogen drugs. However, because of the price of gonadotropins we decided to first prove that P was superior to follicle stimulation drugs, then consider a new study in women with luteal phase defects, but appearing to develop a mature follicle, and then determine, whether a boost of exogenous FSH post mid follicular phase plus P in the luteal phase would be superior to P only. Unfortunately, we never initiated the proposed study.

In the aforementioned study of 100 women comparing exclusive P treatment vs follicle stimulating drugs, if one did not separate them according to whether the follicle attained maturity, or not, different conclusions would have been reached just comparing P only therapy to follicle maturing drugs [3]. Depending on how studies are designed, sometimes erroneous conclusions can be made. In the aforementioned study that separated infertile women according to attaining a mature follicle or not, there was a significantly higher LDPR in those women treated with P vs follicle stimulating drugs where they attained a mature dominant follicle [3].

However, the results would have looked different if the study did not separate the data according to follicular maturation. There was a total of 43 women taking exclusively P in the luteal phase vs 57 taking follicle stimulating drugs. The clinical pregnancy rate for the 43 taking P only during the first 6 months was 27 of 43 (62.8%) vs 24 of 57 (42.1%) taking follicle maturation drugs [3]. If one's bias is that P only is not superior to follicle maturity drugs one could conclude that the differences were not significant, and thus could have been attained by chance alone. In contrast a researcher whose bias is that follicle maturation drugs have a negative impact or that P is simply superior, they may conclude that there was a trend for a negative effect of follicle maturing drugs, and thus P supplementation is superior. In fact, they may then do a power analysis to determine what number of patients would be needed if this difference was maintained to show significance [3].

However, a study without subdividing by follicular maturation would not be a properly designed study because comparing women with luteal phase defect (LPD) who do make mature follicles, using P alone vs follicle drugs, a significant superior benefit for the use of P supplementation was demonstrated [3]. A major experimental flaw in design will be addressed a little later when the author discusses the largest most quoted RCT study to date in determining whether supplemental P reduces miscarriage rates or not [4].

There are some studies that suggest follicle maturing drugs can inhibit adequate inflammatory processes leading to insufficient development of spiral arteries, thus suggesting the possibility that improved fecundity can be achieved in these cases by performing an endometrial scratch to actively increase inflammation [5].

If the concept is correct that one of the main mechanisms involved in allowing the fetal semi-allograft to thrive in a very vascular site with exposure to cytotoxic white blood cells is dependent on the secretion of immunosuppressive proteins e.g., the progesterone induced blocking factor (PIBF), then one must be cautious about studies using other types of progestogens e.g., dydrogesterone or 17-OHP since neither of them increase the secretion of PIBF [6]. This would apply to studies evaluating luteal phase support for infertility, recurrent miscarriage, or pre-term delivery. Also, systematic reviews that included "properly randomized controlled studies' using certain criteria that the authors deem necessary for validity, but included studies that used any other type of luteal phase support than P itself, should be viewed with caution concerning the conclusions that were reached [7].

Despite the fact that oral P raises serum PIBF very well, based on the fact that most oral P is metabolized though first pass through the liver, and thus only a small percent reaches the endometrium, if the concept holds that serum PIBF is mostly from circulating gamma/delta T cells (which may play another role e.g., inhibiting pre-term delivery), however, conception and prevention of miscarriage may depend on luteal secretion of PIBF by the rapidly growing cells of the embryo and placenta, thus the most credible studies would use intravaginal or intramuscular P for luteal phase support, not oral P.

Is Dating Histologic Changes in the Luteal Phase by an Endometrial Biopsy Important in Deciding if the Treating Physician Should Recommend P Therapy or not in the Luteal Phase?

Based on the aforementioned study of 100 infertile patients whose only known defect was an out of phase endometrial biopsy taken during the mid to late luteal phase, if one did make a mature follicle, the recommended treatment would be exclusive use of P in the luteal phase (intravaginal or intramuscular). Follicle maturing drugs (preferably a boost of FSH in the late follicular phase) followed by P in the luteal phase, would be recommended if a mature dominant follicle is not attained [3]. However, what if the endometrial biopsy was in phase? Structural changes of the endometrium that are determined histologically by an endometrial biopsy are moslyt dependent on estrogen inducing nPRs and subsequently to P interacting with nPRs [8,9]. Since PIBF (and other immunosuppressive P induced proteins e.g., the progesterone receptor membrane component-1 protein (PGRMC-1) involve activation of mPRs, women with in phase endometrial biopsies could still have infertility related to insufficient PIBF or PGRMC-1 secreted by rapidly growing fetal-placental cells.

Thus for "unexplained" infertility, for a much less expensive option than IVF-ET, one could still treat the women with P empirically in the luteal phase. Theoretically aging may lead to a greater need for more PIBF to create sufficient blockage of cellular immune rejection of the fetal placental semi-allograft. Thus, we decided that if all known fertility factors seemed normal, including the endometrial biopsy was in phase, we would still empirically treat with luteal phase P, especially if the women had a history of pelvic pain or was age >30 years. We hypothesized that an etiology for unexplained infertility may be insufficient PIBF production in the fetal placental microenvironment to neutralize NK cells and other cellular immune cells from attacking the fetal semi-allograft. As we will discuss later in this perspective, pelvic pain may be an indication of insufficient neutralization of an excessively increased inflammatory state than what is needed in the early luteal phase for uterine artery remodeling to create spiral arteries.

We performed a study of infertile women with unexplained infertility who did not have an endometrial biopsy for histologic dating to be treated with vaginal P exclusively if the dominant follicle was deemed mature. The successful completion of the first trimester with exclusive P treatment was evaluated for 2 age groups <39.9 or 40-45. Women < age 30 were only given P if they had pelvic pain. Based on age and pelvic pain, a mature follicle was obtained in 80% (32 of 40) of women aged <39.9 and 78.2% (26 of 33) in women aged 40-45 [10].

The live pregnancy rate past the first trimester within 6 months of treatment was 71.7% for women <39 who did attain a mature dominant follicle. The average age for the younger group was 32.5 and the average number of cycles treated with P was 4.5. The average length of infertility was 2.3 years [10].

For women aged 40-45, the average age was 42.8 years with an average of 3.1 years of infertility. The average number of cycles of P to achieve a pregnancy was 4.8. The live delivered pregnancy rate within 6 months of treatment was 19.2% [10]. Thus, we no longer use the dated endometrial biopsy in our infertility work-up with the thought that although it may help to determine that some women with infertility or frequent miscarriage could benefit from P support in the luteal phase if the biopsy was out of phase, however, an in phase endometrial biopsy may not predict those women who would still benefit from P supplementation.

Studies Elucidating the Mechanism of How PIBF Suppresses Cellular Immunity and Thus Helps to Prevent Damage to the Fetal Placental Semi-Allograft

There are many types of immune cells that are potentially involved in immune rejection or attack of the fetal semi-allograft when live delivery is not attained. White blood cells that may be involved in immune attack of the fetus includes natural killer (NK) cells, macrophages, cytotoxic T cells, and also dendritic cells. Some studies suggest that NK cells represent 70% of the white blood cells of the fetal placental microenvironment with 20% macrophages and 10% cytotoxic T cells [11]. Studies have demonstrated that P inhibits activation of NK cells [12]. Also, P seems to inhibit activation of macrophages [13-15]. Though dendritic cells are only a minority white blood cell, they peak in number at mid cycle with peak E2 levels and seem to play a role in the immunology of pregnancy [11,12]. P plays a major role in dendritic cell regulation and function [5,16,17]. P seems to suppress inflammatory cytokines e.g., tumor necrosis factor alpha, interleukin (IL)-12, and IL-1 [14,18]. P also suppresses chemokines such as macrophage inflammatory protein 1 alpha and 1 beta and RANTES [19]. There is evidence that many of these immunoprotective events are mediated by the stimulating effect of P on PIBF, which, in turn, converts a TH-1 dominant cytokine environment into a TH-2 dominant cytokine environment [20-22].

Progesterone seems to play a major role in the formation of tolerogenic dendritic cells [23]. Though dendritic cells only represent a tiny percentage of the white blood cell population, there is evidence that interfering with the effect of P in developing tolerogenic dendritic cells results in poor production of CD4 T regulatory cells resulting in poor depth of fetal placental invasion. This, in turn, could cause poor placentation which could lead to pre-eclampsia, pre-term delivery, or intrauterine growth restriction and miscarriage [23]. There is evidence that mPRs and PIBF are the main regulators of these events [24,25].

The Role of P Supplementation with Increased PIBF Production in Preventing 1st Trimester Miscarriage

Based on the aforementioned study that we published in 1988 of 100 consecutive women with more than 1 year of infertility with the sole cause of infertility seemingly to be a luteal phase defect there were 10 total patients who were treated exclusively with

a follicle maturing drug (mostly clomiphene) and conceived, but 6 patients miscarried (60%) [3]. In contrast, out of 41 women treated with P who conceived, with or without a follicle maturing drug, only 2 miscarried (5%) [3]. It was difficult to recruit 100 patients for this study. Though a 60% miscarriage rate vs 5% seems impressive, the most one can conclude from the study is that there may be a trend to prevent miscarriage with supplemental P. Thus, it seems worthy of pursuing an RCT with more power to determine in women who seem to have LPD as the only apparent cause of infertility, if they are more prone to miscarriage if they conceive without supplemental P started in the early luteal phase and continued through the first trimester [3]. As a sub-analysis, one could determine if taking an anti-estrogen drug for 5 days e.g., clomiphene citrate or letrozole, increases the risk of miscarriage by blocking estrogen receptors with the knowledge that estrogen interacting with its receptor leads to the induction of P receptors [8]. One could compare the miscarriage rates in those women using a selective estrogen receptor modulator (SERM) or an aromatase inhibitor to correct follicular maturation vs low dosage gonadotropins with P supplementation in the luteal phase [9].

Another question is whether women with a history of recurrent miscarriage can reduce their risk of a subsequent miscarriage if they are supplemented with P [26]. As previously discussed, taking extra progesterone increased PIBF production both by circulating gamma/delta T cells and rapidly proliferating fetal placental cells [7,27-29]. The PIBF in turn, inhibits TH1 cytokine production which inhibits cellular immunity [27].

A previous study by Yeko et al found that 17 of 18 women not supplemented with P miscarried who had a serum P <15ng/ml [29,30]. Yet one study found that with aggressive P therapy, including a combination of intramuscular and vaginal P, that 70% of pregnant women could complete the 1st trimester with a viable fetus if the serum P was less than 15ng/ml with first evaluation in pregnant women [31].

These studies support the concept that P treatment can stop a probable miscarriage from happening. However, probably only a very small minority of women with recurrent miscarriage have serum P levels so low during their 1st trimester. Thus, if P therapy was only helpful to prevent miscarriage in those women with a history of recurrent miscarriage who have a tendency for very low serum P levels in early pregnancy, one would require a huge number of patients in the study to demonstrate a significant benefit of P. It should be noted, however, that the study by Yeko et al included women whose serum hCG levels may not have been rising properly, whereas in the study by Check et al there was an appropriate rise of hCG when aggressive P therapy was started [30, 31].

There have been many studies both pro and con on the benefit of P to prevent miscarriage [32]. Thus, often to answer a study question, a set of criteria are established by the authors which in their opinions are clinically important. Subsequently, the data from "valid" RCTs could be combined and a meta-analysis is performed. The conclusion by the "latest" meta-analysis could be subsequently changed if another RCT was performed and reached an opposite conclusion. Indeed, a meta-analysis by Oates-Whitehead, Haas and Carrier published in 2003 evaluated 14 clinical trials and they failed to find a significant difference in preventing miscarriages in the P treatment experimental group vs no treatment controls [33]. However, one of the authors or that meta-analysis named Haas, subsequently reached a different conclusion, and that was that taking vaginal micronized P did help reduce miscarriage rates for women with a history of recurrent miscarriage or bleeding in the 1st trimester in 2005 using a different set of criteria for study inclusion [34].

As previously mentioned, a subsequent RCT which was by far the largest RCT ever performed evaluating the efficacy of P to prevent miscarriages was properly randomized, and was multi-centered, (thus eliminating bias from a select patient population by one given group), did not find that supplemental P significantly reduced miscarriage rates [4]. If a meta-analysis would be conducted now and included the PROMISE study of Coomarasamy et al, the conclusion of the benefit of P would change again back to no or little benefit [4]. However, in our opinion, there was a major flaw in the experimental design of the Coomarasamy et al study since the vaginal P was started no sooner than the first positive pregnancy test and even up to 2 weeks from a positive serum beta hCG level [4]. Thus, in our opinion, based on the critical need to make PIBF from the early luteal phase to negate the TH-1 dominant inflammatory state that exists in the early luteal phase (to help develop thin-walled spiral arteries), but would need to be quality neutralized to prevent harm to the fetus was not properly designed because the P was started too late. Failure to convert to a TH-2 dominant cytokine environment by day 6 after ovulation, when there is trophoblast invasion into the endometrium, could lead to impairment of depth of invasion or early injury to the fetus from cellular immune activity. This could lead to infertility if severe, but a subsequent miscarriage if the initial attack injured the fetus but was not immediately lethal.

Theoretically, there are other ways that there may be relatively insufficient P leading to a subsequent miscarriage. The corpus luteum of pregnancy could fail before there has been adequate placental P production. Placental defects could lead to a later 1st trimester miscarriage even if the corpus luteum of pregnancy was making the proper amount of P and ceased making P at the proper time. A short follicular phase, or failure to generate a sufficient rise of serum E2, may impair adequate development of both nuclear and membrane PRs.

Suppressing Excessive Infiltration of Cellular Immune Cells in Addition to Taking Measures to Inhibit their Killing Effect by Supplemental P.

There is one other possible therapy that offers an inexpensive, well tolerated treatment, in addition to supplemental P to prevent a miscarriage. In women prone to miscarriage, there is the possibility that PR development and the amount of P secreted is adequate, but there is excessive infiltration of irritants during the remodeling phase of the uterine arteries shortly after the LH surge related to supranormal increased cellular permeability [5]. This could lead to the development of an excessive number of TH-1 cytokine dominant cellular immune cells that would not be completely neutralized even with maximum production of PIBF or PGRMC-1. Because dopamine functions to decrease cellular permeability, one hypothetical model of successful embryo implantation proposes that the initial inflammatory

state is precipitated by early P secretion by the corpus luteum suppressing dopamine, thus allowing an influx of irritants into pelvic tissues which is needed for normal autoimmune creation of spiral arteries [5,11]. Thus, theoretically medications that release more dopamine may not only help to reduce miscarriage risk by restoring normal cellular permeability, but also ameliorate many other chronic treatment refractory pathological conditions including, but not limited to, pelvic pain if they are also related to increased cellular permeability leading to infiltration of irritants into pelvic or non-pelvic tissues [35-40].

Unfortunately, most of the publications supporting this concept are anecdotal, but, nevertheless, they are very convincing cases. Hopefully these case reports may stimulate interest in a properly designed, well powered, multicentered RCT comparing the efficacy of P alone vs the addition of a dopaminergic drug in reducing the risk of miscarriage (or even for their relative efficacy in correcting infertility). The experimental design should ensure that the supplemental P is started after ovulation.

In this proposed RCT, one should use micronized P started vaginally from early luteal phase to completion of the 1st trimester. Dydrogesterone was one of the progestins that failed to increase serum PIBF levels in our study [6]. However, a meta-analysis of 13 studies with almost 2500 patients suggested that dydrogesterone could reduce the risk of miscarriage [41]. Previously Kalinka and Szekeres-Barto did find that dydrogesterone increased serum PIBF but that was with using the less sensitive immunocytochemistry technique [42]. Schindler, who also conducts PIBF research, concluded that dydrogesterone had benefits in reducing risk of miscarriage [43]. Our study used a more sensitive ELISA technique to measure PIBF [6]. Nevertheless, an RCT comparing vaginal or IM P vs dydrogesterone in preventing miscarriages in women prone to 1st trimester losses could be interesting. Table 1 describes a potential RCT to evaluate the efficacy of P in preventing miscarriage. This could be modified by other centers participating in the RCT who may have additional input to the experimental design.

In the authors' opinion, if establishing a well-designed RCT with enough power to prove efficacy of P therapy is not likely to occur in the near future, the treating physician should ask him/her self if there seems to be potential benefit, based on the knowledge of the effect of P on histological structure and immune factors in promoting fecundity, does it not make sense to treat women with P to prevent miscarriage (or aid in correcting infertility) rather than not treating with P until there is definite proof of its efficacy?

PIBF May Improve Egg Quality

The potential beneficial effect of PIBF in preventing miscarriages that was discussed so far probably refers to the immunomodulatory splice variants inhibiting cellular immune attack of the fetal semi-allograft [44]. IVF studies have documented that top quality embryos have a greater chance of producing a live delivery. Better pregnancy rates are also found with a higher percentage of metaphase II eggs retrieved. As mentioned, the 90kDA parent form of PIBF is associated with the centrosome and thus could play a role in egg quality [44]. Actually, Adamczak et al found that higher PIBF concentrations in follicular fluid at the time of egg retrieval correlated with the formation of better-quality embryos and a greater chance of finding a good quantity of metaphase II egg [45]. Better quality embryos may correlate with less risk of aneuploidy [45].

The Role of P and PIBF in Preterm Labor

As mentioned, we found that serum PIBF correlated with increasing levels of P even in non-pregnant women [6]. Lim et al published data showing that as serum P rises so does serum PIBF across all 3 trimesters [46]. In animals, parturition is initiated by a drop in serum P. However, in humans, the serum P does not drop prior to parturition, but the serum PIBF drops suggesting down regulation of mPRs in gamma/delta T cells and thus relative insensitivity to P in making PIBF [44, 46]. Urinary PIBF concentrations increase to 37 weeks in healthy humans and then they start falling [47]. Thus, parturition can be considered, in a sense, an immune rejection phenomenon because the drop in PIBF shifts the balance from a TH-2 cytokine dominant environment back to a TH-1 pro-inflammatory environment. Lien et al suggests that inflammation in the upper genital tract is very important in the causation of preterm labor [48]. There are several studies suggesting that there is an increase in TH-1 cytokines and a decrease in TH-2 cytokines in the serum and urine in women with preterm labor compared to women with full term delivery [49-52].

Based on our studies of the efficacy of P in inducing PIBF secretion, we would not have thought that treatment with 17 OHP would be a good choice to prevent preterm delivery since it did not increase PIBF levels [6]. However, for a while 17OHP was believed to increase gestational time, and it was approved to prevent preterm delivery. However, a multicenter international, randomized double-blind trial comparing 17OHP to placebo found that 17OHP had no clinical benefit in preventing preterm delivery (PROLONG study) [53].

In another RCT comparing vaginal P to 17OHP, the group taking vaginal P had a later mean gestational age of 37.36 weeks vs 36.34 weeks for 17OHP [54]. Though not achieving a statistical difference, the percent of women who delivered <37 weeks was 31% for vaginal P vs 38% for 17OHP [54]. There could be multiple factors involved in preterm delivery. It would be interesting to see if the addition of P was only helpful in those where supplementing with P increased PIBF or in women with a history of pre-term delivery who had a decrease in serum or urine PIBF levels associated with high risk of preterm delivery. Since supplemental P has no known harmful effects, and may have some benefit in extending gestational age, an interesting research project would be to evaluate PIBF levels in patients already supplemented with P, and measuring serum P at the same time, to answer questions about PIBF resistance to P vs low serum P despite P supplementation as potential factors in the causation of preterm delivery. In the former, possibly potential etiologic factor in causing preterm delivery, improvement of outcome could be achieved by PIBF therapy, and in the latter by being more aggressive with P therapy e.g., adding vaginal suppositories or intramuscular P. PIBF is not available as a therapeutic agent at this time. However, following the determination of the molecular structure and amino acid sequence of the parent 90KDa form and the splice variants (especially the 35kDa form) by Polgar et al, commercial production of PIBF would not be difficult [55].

Table 1: One Proposal for a Meaningful RCT to Evaluate the Efficacy of P In Preventing Miscarriage

1	To gain more power include all women up to age 39.9 that have had more miscarriages than successful deliveries
2	Later one can sub analyze the data as to a) no history of a successful delivery b) one initial success followed by 2 or more losses c) one success sandwiched between miscarriage before and after d) success (1 or 2) at early age followed by 2 or more miscarriages subsequently
3	Sub analyze miscarriage in women <35 vs 36-39 vs losses in both age subdivisions combined
4	only include cases documented to have made a mature dominant follicle
5	If a follicle maturing drug is needed, sub analyze whether a SERM or aromatase inhibitor was used vs gonadotropins
6	Vaginal P or I.m. P or both given from early luteal phase to 12 weeks from conception and the dosage of P should be aggressive
7	The type of P should be pure P not a synthetic progestin.
8	Ethically it may be difficult to set up such a study in women seeking help for infrequent miscarriages with the use of placebo vaginal suppositories. Perhaps if a pharmaceutical company needing an RCT for a new P drug approval, could set up a multi-centered RCT, but then hopefully they would adequately compensate the patients randomized to placebo.

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