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# Combined Dopaminergic Drugs with Supplemental Progesterone to Treat Recurrent Miscarriage and Ulcerative Colitis despite Diminished Egg Reserve

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## ABSTRACT

***Rationale:*** *Chronic inflammation of pelvic tissues related to increased cellular permeability may not only be responsible for diminished oocyte reserve (DOR) but may also contribute to recurrent miscarriage and other co-morbidities.*

***Objective:*** *To determine if treatment with dextroamphetamine sulfate to release more dopamine from sympathetic nerve fibers to decrease excessive cellular permeability, and thus reduce excessive cellular immune activity, coupled with progesterone supplementation from luteal phase throughout the first trimester to increase the amount of the immunomodulatory protein the progesterone induced blocking factor (PIBF) could prevent another miscarriage in a 37-year-old woman with recurrent pregnancy losses.*

***Findings:*** *With this treatment, not only did she conceive in her first treatment cycle and delivered a full-term healthy baby, but the dextroamphetamine markedly improved her ulcerative colitis. Proof that the improvement of the ulcerative colitis was medication related and not merely fortuitous was determined by proving Koch's postulates. The improvement was found to be long-lasting in that she has not had any symptoms of inflammatory bowel disease for 1 ½ years post-partum.*

***Conclusions:*** *Dopaminergic drugs plus progesterone should be considered first in women with DOR and a manifestation of potential excessive inflammation as evidenced in this case by inflammatory bowel disease. This is the second case report of improving treatment refractory ulcerative colitis with dextroamphetamine, which is considerably safer to the patient and more efficacious than the standard immune suppressants.*

## Keywords

Miscarriages, Chronic inflammations, Diminished oocyte reserve.

## Introduction

A woman who has had two or more miscarriages is more prone to having another one in her next conception. There are probably no etiologic factors that are absolute, e.g., that they will inevitably always lead to another first trimester miscarriage. For example, a woman or man with a balanced translocation will definitely have an increased risk of another loss related to a partial trisomy, but still the majority of the conceptions will either be normal or carry the balanced translocation. Though *in vitro* fertilization (IVF) with preimplantation genetic diagnosis (PGT) could lower the chance of another miscarriage for some couples, this is a far too expensive option especially, when considering that no IVF with PGT could still result in a live healthy delivery. Furthermore, there is no guarantee that if a pregnancy ensues following embryo transfer that there still may be a pregnancy loss from some other unidentified factor. If there were no genetic studies on all of the previous pregnancy losses, one cannot say for sure that an imbalanced translocation was the etiologic factor in those miscarriages if this was found in either the female or male partners. Similarly, extrinsic thrombophilia

factors may be the cause of miscarriage especially after ten weeks in the first trimester, or more likely second trimester, related to the presence of anti-phospholipid antibodies (APAs). However, there is still a lot of controversy as to which of the APA's are most important, and what level constitutes an abnormality, and why do they seem to be present sometimes and disappear at other times [1]?.

Intrinsic coagulopathies e.g., women heterozygous or homozygous for factor IV leiden mutation, may be at greater risk for thromboembolic issues and complications of the pregnancy beyond the first trimester e.g., intrauterine growth restriction and preeclampsia. However, the platelets during the early to mid to first trimester are thrombophobic rather than thrombophilia. Thrombophilliia does not start until after ten weeks. Thus, the use of heparin or low molecular weight heparin is not likely to prevent early to mid-first trimester miscarriages [2]. Furthermore, low molecular weight heparin, or even low dosage aspirin, may increase the risk for subchorionic hematomas, and thus cause a first trimester miscarriage [2]. Low dosage aspirin by suppressing some key prostaglandins during the follicular phase may even decrease the chance of conception [3]. As a woman ages, the risk of creating a fetus with aneuploidy related to chromosomal non-disjunction increases. Thus, one can reduce the risk of miscarriages in a woman of advancing reproductive age by performing IVF and PGT for aneuploidy (PGT-a). However, pregnancy rates drop with advancing age also, so this is an expensive option with no guarantee that it will lead to a definite pregnancy or a definite live delivery even if conception occurs with a euploid embryo related to other factors that can cause pregnancy loss. There does not appear to be evidence that miscarriages related to a high predisposition for aneuploidy even exist (except for advancing age) or if so, it is very uncommon and not likely to be solved by IVF-ET with PGT-a [4]. Similarly, there is little evidence to substantiate that susceptibility to infection with bacteria e.g., Urea plasma, is a cause of miscarriage, except possibly in a minority of cases. Thus, there are no convincing studies that prophylactic antibiotic therapy e.g., doxycycline before conception, followed by safer antibiotics for the fetus during the first trimester, are effective methods to significantly reduce the risk of first trimester miscarriage [5]. Possibly, though, removal of bilateral hydrosalpinxes or even unilateral hydrosalpinx could reduce risk of fetal demise [6,7].

Textbooks or summary articles discussing the etiology of miscarriage usually include hypothyroidism. That may be true for very severe cases, but there is no evidence that subclinical hypo thyroidism as detected by a serum thyroid stimulating hormone (TSH) level that is hardly elevated despite a normal free thyroxin (T4) or free triiodothyronine (free T3) level, or even slightly low levels of free t4 or a free t3, would definitely cause a miscarriage. Part of a standard work-up of frequent miscarriage is to evaluate the uterine cavity. Uterine anomalies, e.g., a unicornuate uterus or bicornuate uterus may be a cause of first trimester, or more likely later losses, but they are generally not amenable to surgical repair. Treatment by transferring embryos to a gestational carrier can obviate the problem, but unless a friend or family member volunteers to be the gestational carrier, going through a lawyer or agency is an extremely expensive option possibly costing as much as $200,000 in the United States. However, uterine abnormalities can still result in a successful live delivery [8].

A uterine septum can be a cause of first trimester miscarriage if the fetus implants on the septal wall and subsequently outgrows the blood supply. Thus, in some instances septoplasty can reduce the risk of miscarriage [9]. However, it is not likely to be the cause of repeated losses because there is no reason that the blastocysts would not implant on the uterine wall in other pregnancies. In fact, one study found no decrease in miscarriage rates in women with one previous miscarriage who was diagnosed to have a septate uterus by saline infusion sonography, hysterosalpingogram or hysteroscopy who had a septoplasty prior to her next pregnancy compared to the group randomized to have no surgical intervention [10].

Possibly a large intrauterine polyp may be an etiologic factor in a minority of cases of recurrent miscarriage, and thus removal may help to prevent another. However, in general, there is no evidence that in the majority of cases polyps interfere with fecundity either by causing infertility or causing miscarriage [11]. Similarly, extensive intrauterine adhesions may cause infertility (more common) or miscarriage (less common) where removal may reduce miscarriage rates. However, one must be careful to eliminate other factors causing miscarriage or try other empirical but non-noxious therapies that may reduce risk of miscarriage before hysteroscopic lysis of adhesions especially in menstruating women because in some instances the surgery will worsen the prognosis [12]. It is well known that during the first trimester if one takes mifepristone, a progesterone receptor (PR) antagonist, for just one day, a high percentage of women will miscarry [13]. Thus, for many years it was considered that insufficient progesterone (P) was a likely cause of some miscarriages either because the corpus luteum was inadequately developed, leading to insufficient production of factors controlled by progesterone that are needed for proper implantation six days after ovulation, or insufficient factors that would prevent the human body to immunologically attack the fetal semi-allograft, or a corpus luteum of pregnancy that fails before there is adequate production of P by the placenta [14]. It was believed that though these P induced factors may be needed to even achieve a documented chemical pregnancy, a more severe P deficiency could lead to infertility, whereas lesser degrees of P deficiency may lead to conception but to later fetal demise [14,15]. Thus, for years P supplementation in the luteal phase and during the first trimester was used to treat women with recurrent miscarriage [16]. However as seen in practically every type of medical disorder, there is not usually universal agreement on the efficacy of the etiology of various medical disorders and the treatment of certain pathologies [17]. This applies to the question as to whether corpus luteum inadequacy can be a cause of frequent pregnancy loss, and whether P supplementation can reduce the risk of miscarriage [17].

It is generally considered that the sine que non of scientific studies are randomized controlled, double blinded highly powered, studies. An added plus would be given if there were RCTs that were multicentered. However, even RCTs can differ in their conclusions. This sometimes leads to another group establishing the criteria that they think should be included in a proper RCT, and thus evaluate by meta-analysis in which all of these studies are put together, markedly increasing the power of the study, and hopefully finally providing the answer to the debatable issue. This information trickles down to the vast majority of clinicians in that medical field to help them to develop a basis for diagnosis and /or treatment of certain pathologic states. It becomes frustrating and confusing to the treating physician when at the same time another meta-analysis with different inclusion criteria reaches the opposite conclusion, or if some other RCTs are performed subsequent to a given meta-analysis, and then, even using the same criteria for selection of studies, now reaches a different conclusion. Based on published guidelines and observation of methods of treating recurrent or frequent miscarriages by other infertility specialists or gynecologists, when we are consulted, it seems that the use of P to help prevent another miscarriage has fallen into disfavor. Probably this is related to the publication of the largest RCT that was multi-centered (35 authors), and by far the most highly powered study of its kind which did not show benefit of P supplementation to decrease the risk of miscarriage (65.8% P-treated live delivery pregnancy rate vs 63.3% for controls). This study was published in the very prestigious medical journal, "The New England Journal of Medicine" [17]. Subsequently four years later that same large multicentered group published another RCT also in the N Eng J Med reached the same conclusion about the lack of benefit of P supplementation in women with vaginal bleeding in early pregnancy [18].

The problem with the Coomarasamy study was that the experimental design was considerably flawed. The P was not provided to these patients until they had a positive pregnancy test, or at least within two weeks of the positive pregnancy test! In the discussion section of this manuscript, we will discuss our research to hopefully convince the reader that the critical time to start P supplementation is immediately after ovulation, and then subsequently for several days before implantation to negate attack of the fetal semi-allograft by the cellular immune system. To help rekindle interest in clinicians to once again consider the very inexpensive, well tolerated, P therapy for recurrent miscarriage, we present a very convincing case report. Furthermore, this case report will emphasize a novel treatment with the addition of a dopaminergic drug to further enhance the benefits of P supplementation from luteal phase throughout the first trimester to decrease the risk of miscarriage in those women prone to this problem, especially in the absence of any other known remedial conditions that could be responsible for miscarriage.

## Case Report

This 37-year-old woman presented to our medical facility to get a second opinion on how to achieve a live delivery. She had conceived twice in a seven-month interval, but had two miscarriages. Gestational sacs without fetal poles were observed in both pregnancies by ultrasound. She was advised by the reproductive endocrinologist/infertility specialist, to whom she was referred to by her OB/GYN, that the miscarriages were probably related to aneuploidy. As far as treatment to prevent another miscarriage, the infertility specialist advised her to utilize donor eggs and following fertilization with her husband's sperm to have them transferred back into her uterus. The basis for this recommendation was that she had diminished oocyte reserve (DOR) as evidenced by a serum anti-mulleran hormone (AMH) level of 0.3 ng/ml. They advised her that though she was only 37 years old, her physician believed that her eggs have the same quality as women $\geq$ 45. She was further advised that her chances of having a live baby with her own eggs would be less than 1%. However, if she wanted to still try with her own eggs, they would advise IVF with PGT-a, and only transfer euploid embryos which the specialist advised her would be very unlikely. She was not happy with the suggestion by the infertility specialist and came to us for a second opinion. In contrast to the opinion of her first consultant, we advised her that following the tenets of the FSH receptor upregulation technique (which has been previously described in detail) and with the use of luteal phase support with P, that she would have a reasonably good prognosis of having a live baby through natural intercourse [15,19,20].

Though she denied dysmenorrhea or other types of pelvic pain restricted to certain time periods of the menstrual cycle, she was advised by our group that increased pelvic inflammation may be to the cause of the DOR and the two miscarriages. The rationale used to make that statement was first based on the absence a known etiology for DOR in that she and her husband had a normal chromosome analysis, and she denied a history of pelvic surgery or radiotherapy to the abdomen or chemotherapy, or family history of early menopause to explain the DOR, leaving ovarian inflammatory damage as the most likely etiology for the DOR. Though she denied pelvic pain, it is well known that the presence of endometriosis may be associated with DOR even in those not compromised further by surgery to remove the endometriosis [21,22]. Endometriosis is usually associated with pelvic pain, but increased cellular permeability with the infiltration of excessive irritants into the pelvic tissues causing inflammation may be the cause of the pain rather than the endometriotic implants per se. The endometriosis may actually be the result of increased cellular permeability allowing menstrual tissue to escape to ectopic areas. This would explain why some women have severe pain, but no endometriosis found, or even following the removal of endometriosis some women experience quick return of pain even when second look laparoscopic failed to find recurrence [23,24]. Pelvic pain is just one manifestation of the increased cellular permeability syndrome [25]. The inflammation marker BCL6 is present in a high percentage of women with endometriosis [26]. Sometimes when laparoscopies are performed for unexplained infertility, extensive endometriosis is present without a history of pelvic pain.

Though this 37-year-old woman denied pelvic pain, she did have one manifestation of the increased cellular permeability syndrome, and that was ulcerative colitis. She was diagnosed with ulcerative colitis by colonoscopy, which was performed to evaluate her symptoms of hematochezia associated with 10-12 bowel movements per day. She would get severe abdominal pain with the diarrhea. The bowel inflammation eventually was controlled with high dosages of prednisone, which she took for three months. Eventually over the seven years from initial diagnosis until the time she consulted our practice, the ulcerative colitis had been improved by taking mesalamine and avoiding certain food elements that caused immediate exacerbation of the hematochezia, frequent bowel movements, and abdominal pain. The worst offending food irritant was red meat. With diet and mesalamine, she was reduced to 3 painless bowel movements per day without hematochezia or abdominal pain. However, about twice a year, she would get flare-ups of the frequent bowel movements, hematochezia and abdominal pain which generally would dissipate after two weeks of high dosage prednisone.

We explained to her about the controversies of using P to prevent miscarriage, but presented our views as to why this P supplementation could reduce her risk of pregnancy losses [17-19,27,28]. We also suggested that we treat her with the dopaminergic drug dextroamphetamine sulfate, which would work in conjunction with the P to reduce potential excessive cellular immunity that may cause miscarriage through immune rejection of the fetal semi-allograft. We advised her that not only have we found dextroamphetamine sulfate to marked ameliorate inflammatory bowel disease (when it was associated also with classic types of pelvic pain, dysmenorrhea, and mittelschmerz) but also, when, similar to her care, the gastrointestinal symptoms did not seem to be associated with pelvic pain and the menstrual cycle [29-32]. Furthermore, we have had cases where there were multiple miscarriages with P supplementation and follicle stimulating drugs even with IVF-ET where addition of dextroamphetamine sulfate resulted in a live delivery [33].

This 37-year-old woman had regular menstrual cycles. According to the principles of the FSH receptor up-regulation technique for women with DOR but regular menses (ie to treat without follicle maturing drugs but just P in the luteal phase in women trying to conceive naturally as long as the dominant follicle reaches an average size of 18-24mm with a serum estradiol of > 200 pg/ml and as long as there was adequate follicular phase length, this patients was treated exclusively with P because she attained this aforementioned follicular maturation criteria [34,35]. She was treated with 400 mg P vaginal suppositories upon awakening and before sleep plus 200 mg of oral micronized P. At the initial consult, she was treated with dextroamphetamine sulfate 9.4 mg 2x/day (given as amphetamine salts immediate release tablets 15 mg 2x/day). She had been on 18.8 mg AM and 9.4 mg at noon during her follicular phase in her first treatment cycle with P. She conceived in her first treatment cycle and subsequently delivered a full-term healthy boy.

Late in the second trimester, the OB-GYN convinced her to stop the dextroamphetamine. However, her diarrhea returned so after delivery she resumed the dextroamphetamine. The baby is now 15 months old, and the patient continues on dextroamphetamine. She reports no symptoms of ulcerative colitis. She has had improvement of the other manifestation of the increased cellular permeability syndrome- including backaches and chronic fatigue [36-40].

## Discussion

There were several objectives of the authors in writing this manuscript

1. To provide a brief review of possible standard and therapeutic options for treating recurrent miscarriages.
2. To rekindle interest in physicians to use P supplementation for women with recurrent miscarriages. Stimulation of interest in using P to prevent miscarriages was hoped to be accomplished by a) presenting flaws in experimental design in the aforementioned well promulgated highly powered multicenter RCT by Coomarasamy et al. that seemed to steer physicians away from supplemental P therapy b) presenting an experimental model based on multiple previous research studies that helped to formulate the necessities for proper embryo implantation c) to support the concept of the beneficial action of P by presenting other good studies that support the use of P to reduce risk of miscarriage, but at the same time to present a new case report that will entice physicians to recommend this therapy again, not only for miscarriages, but also infertility.
3. Stimulate interest in physicians to consider the use of dopaminergic drugs to help prevent miscarriages and promote its use for treating infertility.
4. To make physicians aware of the very common, but not well-known, condition responsible for many disorders including miscarriage, infertility, DOR, but also a multitude of different conditions that will respond very well to inexpensive, well-tolerated dopaminergic drugs e.g., dextroamphetamine sulfate, or even possibly cabergoline [25,41].
5. To make physicians aware that women with DOR when treated with the right protocol have only a slightly lower chance of conceiving than their age peers with normal oocyte reserve [42-45]. Furthermore, this case report serves to demonstrate that conceiving in a natural cycle despite DOR, and slightly advanced age, is possible with normal intercourse and without assisted reproductive procedures (although performed with the proper stimulation protocol IVF-ET could increase the live delivered pregnancy rate two and a half fold) [42-47].
6. To present a second reported case of ulcerative colitis that responded the best to treatment with dextroamphetamine [31].

An experimental model based on previous research is presented table 1

A hypothetical model of how successful table 1 human embryo implantation occurs.

1. Rising estradiol (E2) induces P receptors (PRs) in the endometrium [48].
2. Rising estradiol (E2) increases dendritic cell proliferation [49].
3. The early progesterone secretion by granulosa- these cells stimulated by the LH surge causes the secretion of mucin-1 which coats the endometrial cavity, and thus prevents the day 3 embryo from attaching to the endometrium on day 3 when it reaches the uterine cavity.
4. The dendritic cells help to make a rift in the mucin-1 coating exposing endometrium by day 5 and thus allowing attachment of the blastocyst to the endometrium [49].
5. Certain thick-walled uterine arteries are designated for re-modeling to create thin-walled arteries called spiral arteries that will allow nutrient exchange between mother and fetus [49].
6. The remodeling is accomplished by autoimmune attack of the thick walls of these designated uterine arteries, which is enhanced by P blocking dopamine-allowing infiltration of irritants into the pelvic tissues. Dopamine functions to diminish cellular permeability [49].
7. The fetus is not in an immunologically privileged site and now the presence of the semi-allograft is even in more peril by the enhancement of invading cellular immune cells by P blocking dopamine
8. Neutralization of the killing effects of the cellular immune cells is accomplished by the secretion of immunomodulatory proteins especially the progesterone induced blocking factor (PIBF) which is stimulated by P in membrane PRs and is secreted by cells of the fetal placental unit (embryonic cells, mesenchymal cells, and trophoblast cells and circulating gamma/delta T cells) [50-58].
9. Pelvic pain is not normal, and is usually associated with increased absorption of irritating elements causing excessive inflammation, and thus the need to either increase PIBF production above normal or decrease the excessive permeability to decrease the cellular immune activity.
10. Chronic excessive inflammation action may lead to oocyte destruction and thus premature ovarian insufficiency or premature ovarian failure (apparent menopause).

Based on this working model (which may be mostly correct, partially correct, or only slightly correct), a therapeutic strategy can be developed, which over the years seems to have achieved a large number of live deliveries similar to the patient reported.

Treatment strategy based on this model of successful implantation, and where correctible defects may occur but may vary from cycle to cycle are as follows: For women with regular menses, if the serum estradiol does not reach 200 pg/ml, follicular maturation drugs should be given. Inadequate peak serum E2 at peak follicular maturation could cause infertility or miscarriage by low E2 indicating inadequate number of granulosa-these cells with less P production during the luteal phase. Alternatively, inadequate E2 levels may inhibit adequate development of PRs in the endometrium. If serum E2 attains 200 pg/ml, no follicular validation drug may be needed [20]. A study of women whose only detect diagnosed as a cause of infertility was an out of phase endometrial biopsy found 24 of 31 conceiving in six months with exclusive treatment with luteal phase P and only 1 miscarried vs only 3 of 27 conceiving with follicle maturing drugs with 2 of 3 having a miscarriage [54]. In contrast, for women not attaining a mature follicle, P alone allowed 3 of 10 to conceive with no miscarriage, 7 of 10 with follicle maturing drugs achieved pregnancies but 4 had a miscarriage [54]. However, when both follicle maturing drugs and P in the luteal phase were given this 14 of 20 conceiving but only 1 miscarriage [59]. For women with a history of miscarriage and pelvic pain, dextroamphetamine sulfate, or possibly cabergoline (both dopaminergic drugs) should be added to P therapy or follicle maturing drug therapy plus P to releasee more dopamine from sympathetic never fibers to diminish potential increased cellular permeability [24,41]. Experience has found that dextroamphetamine sulfate is superior to cabergoline in relieving pelvic pain and other manifestation of the increased cellular permeability syndrome. The amphetamine should be continued throughout the first trimester (along with the P) but dextroamphetamine can be stopped if there were no other pathological morbidities that may return (e.g., ulcerative colitis as seen in this patient or other manifestation of the increased cellular permeability syndrome e.g., headaches, urticaria, severe fatigue, etc.) [60].

If there is DOR and a follicle maturation defect, FSH injection in small dosages should be given from mid to late follicular phase when the serum FSH is closer to normal to prevent down-regulation of the FSH receptor leading to lower pregnancy rates [20]. If there is normal ovarian reserve, clomiphene or letrozole or letrozole plus P has been used with success. However, because of the anti-estrogen effect of clomiphene or letrozole, and potential interference with E2 induction of P endometrial receptors, our preference would be to use a boost with low dose FSH in mid to late follicular phase to correct follicular maturation defects.

We prefer vaginal P or IM P as the main type of P to be used. Synthetic oral progestins do not cause a rise in PIBF levels in contrast to P [61]. Using these oral progastrins may not have shown benefit for preventing miscarriage by not stimulating immunomodulatory proteins. This could explain why some RCTs failed to show benefit of luteal phase support to prevent miscarriage especially if synthetic progesterone e.g., depo-17hydroxyprosesternol [61]. Oral micronized P does raise serum PIBF from circulating gamma/delta T cells. However, because 90% of oral P+is metabolized through the first passage through the liver, the uterine P concentration may be insufficient to stimulate PIBF made by the cells of the fetal- placental unit. We frequently add oral micronized P if we want to maintain P throughout the pregnancy since there is some evidence that a decrease in PIBF rather than P in the last trimester can cause premature delivery. 17 hydroxy progesterone does not raise serum PIBF, and thus we prefer P rather than 17-OHP to prevent pre-term delivery [61-64].

Though an out of phase endometrial biopsy taken in the luteal phase, or a low mid-cycle serum P level, or failing to attain a mid-luteal homogeneous hyperechogenic endometrial echo pattern can be useful in determining if a woman should be treated with supplemental P, these tests could still be normal, but a miscarriage could still be related to inadequate PIBF production to suppress cellular immune response against the fetal semi-allograft [65]. Thus, we do not rely on these tests to determine who should be supplemented with P or not [61]. Even if a previous miscarriage has been documented to be associated with aneuploidy of the fetus, there is no harm in adding supplemental P in case of another fetal demise, only this time, with a fetus with normal chromosomes.

There is evidence that cancer cells use the same PIBF immunomodulatory proteins that require membrane PRs for its production [66-69]. Indeed, the use of PR antagonist have demonstrated marked palliative benefits with considerable extension of life in patients very advanced cancers with no known treatment options remaining [69-74]. Though one may have doubts whether using P to stimulate more PIBF to immune rejection of the fetal semi-allograft was responsible for the prevention of a miscarriage in a given treatment, there is little question that blocking the PR, and thus PIBF, can provide a longer better quality life to end stage cancer patients despite the anecdotal nature of the reports and the absence of a large multicentered RCT related to the convincing evidence of case reports. Though luteal phase endometrial biopsies for dating the endometrium seem less common in today's practices performing a biopsy to look for inflammatory plasma cells, measuring CD 138, or even better, BCL6 is more common today. There are some infertility specialists advocating performing laparoscopies to look for and treat endometriosis if there is a positive test for the endometrial BCL6 marker. The benefit of removing endometriosis to improve fertility is also a debatable subject with different RCTs analyses reaching different conclusions [75-77]. Though our own studies favor improving fecundity by removing endometriotic implants, because of surgical risk and possibly neutralizing the damaging effects of increased cellular immune cells (by making more PIBF) we favor adding a dopaminergic drug to the P supplementation over surgery [32].

In the case reported here, despite the marked clinical improvement of the ulcerative colitis, her gastroenterologist did not agree to prescribe the dextroamphetamine sulfate once she delivered. Thus, the patient had to return to our medical practice every three months to receive the amphetamine therapy. OB-GYNs or fertility specialists treating miscarriages or infertility with sympathomimetic amines e.g., dextroamphetamine sulfate, may have to be prepared to be the physician treating other manifestations of the increased cellular permeability syndrome after delivery that also responded to this dopaminergic drug because of the reluctance of various specialists to use a more effective and safer drug if it is an off-label use.

In summary, our hope is that our objectives have been met, and this manuscript reports the second case of ulcerative colitis responding very well to a therapy not known to the majority of treating physicians and that is with dextroamphetamine sulfate. In so doing, we hope we have made the readers more aware of the increased cellular permeability syndrome. Though we have seen more severe cases of ulcerative colitis that responded to dopaminergic drugs, we chose this case report to make physicians in the medical field aware that autoimmune DOR is not necessarily only seen in women with symptoms of endometriosis, but they may have various other medical problems associated with the increased cellular permeability syndrome.

In summary, by reporting this case, we hope that we have made physicians aware that not only are successful pregnancies possible with DOR, but they can happen quickly and without the need of expensive IVF options, or even worse, extremely expensive use of donor eggs so that the female partner does not conceive a child with her own phenotypic features. Most of all, the hope is that physicians treating patients with recurrent miscarriages, realize the benefit of using P at the proper time (which is after ovulation not with the first positive pregnancy test as seen in the Coomarasamy et al. study) [28]. Even if P was given at the right time and the right amount with the patients chosen by their selection criteria with more than 60% of the controls in the Coomarasamy study having a live baby, it would take a huge progesterone study, considering that other causes of miscarriage could occur in the P treated group, e.g., aneuploidy, to demonstrate a significant difference to actually refute the Coomarasamy et al. study. Nevertheless, subsequent to this study, Mary Stephenson et al did show that taking P from early luteal phase did reduce miscarriage rates in women with recurrent pregnancy loss [78-80].

Though we emphasize that the best success in reducing the miscarriage rate is to start P in the early luteal phase, aggressive P therapy in the early 1$^{st}$ trimester can be effective depending on the severity of the P deficiency Yeko et al. found that 17 of 18 women had a miscarriage if the serum P during early pregnancies was < 15 ng/ml [81]. However, we found that aggressive P therapy (vaginal and intramuscular together) decreased the miscarriage rate to 30% if women whose serum P while pregnant was <15 ng/ml [82]. Even with a serum P < 8ng/ml in early pregnancy, aggressive P therapy reduced almost inevitable miscarriages to 60% [83-85]. Finally, over the years, we have seen many treatment refractory cases of ulcerative colitis to respond to dextroamphetamine sulfate but they were not reported. Thus, this is the second case reported of marked improvement of ulcerative colitis with dextroamphetamine sulfate treatment [31]. Hopefully, this case report will make physicians more aware of the increased cellular permeability syndrome and consider treating with dextroamphetamine sulfate for the various pathological manifestations of this syndrome [60]. This condition is not limited to females.

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presented at any scientific meeting or published in part or whole in any other journal. This is the first submission of this case.

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