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Correction of Treatment Refractory Infertility and Severe Constipation Following Treatment with Supplemental Progesterone and a Dopaminergic Drug

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ABSTRACT

Rationale: *Infertility may be related to an exaggerated cellular immune response during the luteal phase that is normally needed to remodel some of the thick-walled uterine arteries to create thin-walled spiral arteries. This excessive inflammatory response may cause immune rejection of the fetal semi-allograft leading to infertility.*

Objective: *To determine if the combination of luteal phase progesterone supplementation to stimulate greater secretion of the immunomodulatory protein called the progesterone induced blocking factor (PIBF) and daily treatment with the dopaminergic drug dextroamphetamine to release more dopamine to decrease excessive cellular permeability in order to prevent excessive infiltration of irritants into pelvic tissues causing excessive inflammation could correct a long term infertility problem in a woman with diminished oocyte reserve and symptoms of the increased cellular permeability syndrome.*

Finding: *By treating with supplemental vaginal P in the luteal phase as well as dextroamphetamine daily, a woman with DOR and secondary unexplained infertility for five years was able to conceive on her very first cycle of dextroamphetamine and P supplementation, and delivered a live full-term baby. Furthermore, the dextroamphetamine completely corrected her very severe constipation and abdominal pain. It should be noted that her only conception occurred after two years of primary infertility on her second in vitro fertilization embryo transfer (IVF-ET) cycle. Furthermore, she failed to conceive for her second pregnancy for four additional years trying naturally and failed after two more IVF-ET cycles.*

Conclusions: *Dopaminergic drugs should be considered to be employed besides P (three IVF cycles with P supplementation without dopaminergic drugs failed to achieve a pregnancy) especially in women with some manifestation of the increased cellular permeability syndrome, e.g., unexplained DOR and pathological constipation. This is the second case of treatment-resistant severe constipation and abdominal pain treated with dextroamphetamine. This case also emphasizes that 1) mild male factor problems do not necessarily require intrauterine insemination or IVF-ET, 2) successful pregnancy with DOR is possible with a woman's own oocytes and does not require IVF-ET with or without pre-implantation genetic diagnosis testing.*

Keywords
Diminished oocyte reserve, Dopaminergic drugs, Increased cellular permeability syndrome, Progesterone supplementation, Severe constipation.

Introduction

There are many causes of why some couples fail to conceive despite having intercourse at the proper time [1]. Some of these infertility factors include ovulation disorders which can include women who are anovulatory. These cases of anovulation can be divided into those with normal estrogen and those with estrogen deficiency [2,3]. Those with estrogen deficiency and amenorrhea can be divided into those with a hypothalamic/ pituitary disorder with insufficient luteinizing hormone (LH) and follicle stimulating hormone (FSH) stimulation to the ovaries, or may be related to a hypergonadotropic state related to oocyte depletion (diminished oocyte reserve or DOR) [4,5].

Women with regular menses may have subtle ovulation defects. A woman may release the oocyte before the follicle is fully mature, where a peak estradiol (E2) of 200 pg/ml or more is not attained before the egg ruptures out of the dominant follicle [6]. Another subtle defect is when a woman attains a dominant follicle, but the oocyte fails to release from the follicle before the serum progesterone exceeds 2 ng/ml. This is known as the luteinized unruptured follicle (LUF) syndrome [7-9]. A slight variation of LUF syndrome is known as premature luteinization [10]. This is where the progesterone rises above 2 ng/ml as the follicle size continues to enlarge and the serum E2 continues to rise [10].

Anovulation with a normal estrogen can occur without menstruation (amenorrhea), may occur but less frequent (oligomenorrhea), or may occur and bleed more frequent (menometrorrhagia or just metrorrhagia). Technically, anovulation may occur with regular menses if there is LUF syndrome or premature luteinization. However, with regular menses, patients may have ovulation disorders other than LUF. They may fail to secrete sufficient progesterone by the corpus luteum causing infertility by failure to present the proper endometrial milieu for proper implantation.

Dating back over 50 years, there was the generalized belief that a defective corpus luteum can be the cause of infertility or miscarriage. This condition was referred to as a luteal phase defect (LPD). Noyes et al. determined histologic changes that occurred each day after ovulation [11]. One of the many considerations for methods diagnosing infertility related to an LPD, was to perform an endometrial biopsy from 7-11 days after ovulation. LDP was diagnosed if the endometrial biopsy dated more than 2 days early [12].

For decades the timed endometrial biopsy was a standard diagnostic procedure to diagnose not only one of the causes of infertility in a couple, but also to help decide on a treatment. One of the popular treatments for LPD was the use of a follicle stimulation drug, e.g. oral clomiphene citrate, or some other follicle maturation drug, e.g., injectable gonadotropins [13,14]. This was based on the fact that when anovulatory women were treated with clomiphene citrate, the mid-luteal serum progesterone (P) levels generally were increased higher than that of the normal ovulatory women [14]. Furthermore, the lack of P secretion by the corpus luteum may have been related to inadequate development of the dominant follicle, and thus an inadequate number of granulosa-theca cells causing the low P levels during the luteal phase [13,14].

However, another choice for treating a P deficiency is to provide extra P supplementation after ovulation [15]. We had determined in an unpublished study that most fertile women attain a mid-cycle dominant follicle of 18-24 mm with a minimum serum estradiol of 200 pg/ml. We evaluated 100 women with a minimum of one year of infertility who had patent fallopian tubes, regular menses, a rise of serum P in the luteal phase, no evidence of LUF, and whose male partner had a normal semen analysis with a post-coital test was showing sperm with progressive movement. The only infertility factor identified was an out of phase endometrial biopsy [16].

We determined that 58 of 100 women, despite an out of phase endometrial biopsy, did attain a mature dominant follicle [16]. The clinical pregnancy rate for the 31 women randomized to exclusive treatment with P vaginal suppositories in the luteal phase over a six-month period was 73.4% (24/31) with only one miscarriage. In contrast, the 6-month clinical pregnancy rate for 27 women taking follicle maturing drugs only (either clomiphene citrate or human menopural gonadotropins) was only 11.1%. Two out of three of these women miscarried so only 4% delivered a live baby [16].

On the other hand, women who ovulated, but never attained a serum E2 of ≥ 200 pg/nl, only had a 25% clinical and live delivered 6-month pregnancy rate (3/12) with exclusive luteal phase P therapy. Follicle maturing drugs, allowed a 70% clinical pregnancy rate (7/10) but since 4 of the 7 miscarried, the 6-month live delivered pregnancy rate was only 30% [16]. However, the 20 women who were treated with follicle maturing drugs in the follicular phase and vaginal p in the luteal phase had a 70% clinical pregnancy rate (14 of 20) but only 1 miscarried [16].

One theory to explain this outcome is that based on the knowledge that estradiol is needed to develop P receptors in the endometrium, the lower success rate with luteal P supplementation in women not attaining a mature follicle was related to inadequate physiologic effect of P due to inadequate development of P receptors in the endometrium [17].

We noticed that when anovulatory women were stimulated with follicle maturing drugs, a high percentage showed LPD by endometrial biopsy, which was corrected by supplemental P [18-20]. Thus, we interpreted that in the aforementioned 100 woman small randomized study that the follicle maturing drugs for women not attaining a mature follicle helped to induce an increase in endometrial P receptors but still did not improve the luteal phase factors sufficiently. There was a 57% miscarriage rate when

supplemental P was not added, but the miscarriage rate was only 7% with P added [16].

Though one could argue that the anti-estrogen effect of clomiphene citrate could block the effect of E2 in inducing P receptors, we have seen supplemental P decrease miscarriage rates in gonadotropin stimulated cycles where there would be no potential blocking effect on the E2 receptor [19]. Theoretically, however, clomiphene could adversely affect the E2 receptors and would not be compensated by the higher rise in serum E2 than typically seen in natural cycles. Therefore , when women had mature follicles, but the endometrial biopsy was more than two days out of phase, the potential adverse effect of follicle maturing drugs, coupled with very satisfactory results with just P supplementation in cases we consider as pure luteal phase defects, our policy is not to combine follicle maturing drugs in the follicular phase plus P in the luteal phase if the dominant follicle achieves maturation criteria. One exception would be if one wants to add the potential advantage of releasing more eggs, especially in circumstances e.g., where there may be a greater chance of non-disjunction of chromosomes, as seen in women of advancing age, leading to aneuploidy of the embryo. The oocyte chosen out of a cohort of antral follicles may not be one of the oocytes in the cohort that is chromosomally normal [16].

The group of women we reported in the 100-woman study with LPD as their exclusive infertility issue were selected because they had infertility [16]. We also found a decrease in miscarriage rate not only in anovulatory women taking follicle maturing drugs but also in women with a history of recurrent miscarriage and women with endometriosis [16,18-21].

For infertile women, if all factors involved in normal conception appear normal, including an in phase endometrial biopsy in the luteal phase, what treatment options are available for cryptic infertility [22]. One possibility is that there is a need for extra P supplementation even if the mid to late luteal phase endometrial biopsy is normal. This could be related to failure of the P secreted by the corpus luteum to suppress the cellular immune cells from attacking the fetal semi-allograft. This could be related to not making a sufficient amount of immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF). These immune modulatory proteins dampen the killing effects of various immune cells including natural killer (NK) cells [23-27]. Supplementing more P has been demonstrated to markedly increase PIBF levels both in the circulating gamma/delta T cells and in the fetal placental microenvironment from embryonic cells, mesenchymal cells, and trophoblast cells [28-32].

Many infertility specialists for unexplained infertility would recommend in vitro fertilization-embryo transfer (IVF-ET) possibly even with intracytoplasmic sperm injection (ICSI) (in case of potential failed fertilization) in the circumstance of cryptic infertility. Unfortunately, IVF-ET is extremely expensive. The use of ICSI adds extra expense, and if the eggs do fertilize, this commits the patient to continue IVF-ET with ICSI with the assumption of non-fertilization as their cause of infertility. However, we would recommend conventional oocyte insemination first, because if this showed failed fertilization, the couple would know that IVF-ET with ICSI would be their best option in their pursuit of a baby. With good fertilization, the couple could try other "experimental options" e.g., luteal phase P supplementation, despite an in phase endometrial biopsy, hoping that the problem was insufficient PIBF to neutralize the cellular immune system with correction by supplemental P. Of course, they could try the supplemental P option even before proceeding with even one IVF-ET cycle, which makes more financial sense.

Thus, one inexpensive option would be to treat empirically with supplemental P, in view of evidence that with advancing age there may be a need for extra P to prevent immune rejection of the fetal semi-allograft. We gave all women aged 30 or above extra P in the luteal phase usually by vaginal route [27]. There is evidence that pelvic pain may be associated with increased cellular permeability allowing more absorption of irritants causing an excess amount of inflammation above the amount normally needed to create spiral arteries. This increase in inflammation may require a higher production of PIBF to neutralize the excessive number of NK cells or macrophages and cytotoxic T cells from attacking the fetal semi-allograft. Thus, we decided to treat all women with pelvic pain with luteal phase P even if they were under age 30 [33,34].

Physicians have been taught that the best studies on which to base their practice procedures are randomized controlled trials (RCTs). RCTs have even more meaning if they are multicentered to eliminate the possibility of a skewed study population. Unfortunately, some RCTs reach opposite conclusions. Then meta-analysis is performed with the hopes of revealing the proper therapy with the data favoring one treatment modality over another. Unfortunately, it is not uncommon for subsequent RCTs to be performed, and now the meta-analysis reaches the opposite conclusion of the previous meta-analysis. Thus, it becomes important for the infertility specialist to be aware of the conclusion of many studies, and decide themselves as to what not only makes the most sense, but would have the least side effects, and not to cause the patient financial harm [35].

For example, it is common practice for infertility specialists to empirically treat the infertile couple whose fallopian tubes are patent, and where the male partner has an apparent normal semen analysis, to treat the women with a follicle maturing drug e.g., clomiphene citrate or letrozole, and perform an intrauterine insemination (IUI). Our own studies failed to demonstrate any benefit of performing an IUI when the semen analysis is normal, and the post-coital test is adequate [36]. Of course, it is possible that the use of clomiphene citrate or letrozole could create a hostile cervical mucus leading to a poor post coital test in which IUI would be appropriate [37]. Nevertheless, based on our own aforementioned studies in the 100-couple study, because 58% did make a mature follicle even when a luteal phase defect was detected by endometrial biopsy, it would seem better not to add

empirical selective estrogen receptor modulators or aromatase inhibitors [16]. Often times, follicle maturing drug treatment is not supplemented by P in the luteal phase in other practices, which, based on our studies, would lead to a higher miscarriage rate even in those who would have demonstrated a follicular maturation defect (if those studies had even been performed).

It is not unusual in cases of "unexplained infertility" for infertility specialists to recommend IVF-ET right from the beginning, or after a few failures with follicle maturing drugs and IUI. Sometimes one sees success for the very first treatment cycle. Could the IVF-ET be successful because of bypassing a subtle tubal defect, or correcting fertilization failure by exposing the egg to a lot more sperm than occurs naturally, or overcoming possible fertilization failure by performing IVF-ET with ICSI? However, another possibility is that IVF, with either a fresh or frozen ET cycle, achieved a successful pregnancy merely by the use of luteal phase P (which is used in almost 100% of IVF-ET cycles). Thus IVF-ET could be a very expensive way to treat with luteal phase P.

Though P supplementation may sometimes be sufficient to neutralize the killing effects of the hypothetical increased cellular immune activity in the fetal-placental microenvironment during the luteal phase, sometimes excessive cellular immune activity is still present leading to immune destruction of the fetus with its foreign paternal antigens. Since there is evidence that P purposely causes the increase in cellular immunity to facilitate uterine artery remodeling to form spiral arteries by blocking dopamine (dopamine decreases cellular permeability), perhaps dopaminergic drugs could relieve pelvic pain and improve fecundity [33,34,38]. In fact, treatment with the dopaminergic drugs dextroamphetamine sulfate and cabergoline have proven to be very effective for marked reduction in treatment resistant pelvic pain [39-45]. Even very long term vulvovaginitis and vaginismus have responded quickly and quite effectively following treatment with dextroamphetamine sulfate [46-47]. Interestingly levo-dopa has proven very effective for vulvar pain as well [48].

There is evidence that dextroamphetamine sulfate can improve infertility especially in women with pelvic pain or other manifestations of the increased cellular permeability syndrome even those who are being treated with IVF-ET with P supplementation. Women with pelvic pain undergoing IVF-ET who received dextroamphetamine sulfate for pelvic pain had even higher pregnancy rates than their age peers who did not have pelvic pain and therefore were not given this dopaminergic drug [34].

One question that arises is whether an increased state of endometrial inflammation can lead to miscarriage even despite IVF-ET and supplemental P. This question is not likely to be answered by an RCT because RCTs are generally expensive, and the financial support is usually provided by pharmaceutical companies trying to gain approval for a new drug. The use of dextroamphetamine sulfate for pelvic pain, infertility, miscarriage, and other conditions is considered an off-label use, and there is very little likelihood that the pharmaceutical manufacturer would fund an RCT especially since the patent for the brand expired long ago. Thus, a convincing case report may influence physicians to consider treating with a dopaminergic drug to prevent miscarriage despite the use of supplemental P. There has been such a convincing case report published where a successful live delivery occurred with the addition of dextroamphetamine sulfate despite repeated miscarriages with IVF-ET and P supplementation [49].

A case is now presented where convincing evidence is provided that the combination of supplemental P and dextroamphetamine helped to achieve a live full-term delivery in a natural cycle in a case of refractory infertility with multiple failures to conceive despite IVF-ET and P supplementation. In addition, this case will be the second report of the beneficial effects of dopaminergic therapy for very severe treatment refractory constipation [50].

Case Report

The patient presented with two years of infertility at age 29 to another reproductive endocrinology/infertility practice. Her menstrual cycles were regular every 28 days. A hysterosalpingogram was performed and demonstrated bilateral tubal patency. The infertility center concluded that the problem was related to a mild male factor problem with slightly low sperm concentration and motility and recommended in vitro fertilization embryo transfer (IVF-ET) and ICSI. She failed to conceive following her first IVF-ET-ICSI cycle but was successful on her second and she delivered a live baby. However, she failed to conceive naturally for the next four years, and she also failed to conceive despite two more IVF-ET-ICSI cycles. The four total IVF cycles led to 13 total embryos transferred (fresh and frozen) leading to only one live delivery.

Though she did not have a high fertilization rate despite ICSI (1st cycle 2 of 5, 2nd 4 of 8, 3rd IVF cycle 5/15 and 4th cycle 2 of 11), she wanted to try naturally because she was financially depleted. Despite the low fertilization rate, she had possibly four pregnancies in natural cycles that showed a positive home pregnancy tests that were not confirmed by subsequent serum beta human chorionic gonadotropin levels.

Though this 32-year-old woman did not have dysmenorrhea, she had over 10 years of severe abdominal pain with very severe constipation with bowel movements generally having a 2–3-week interval. We thus recommended not only treatment with vaginal P (400 mg AM and before bedtime) but also dextroamphetamine sulfate because we believed that the constipation could be related to insufficient dopamine secretion leading to the pathological constipation [50]. Even though she denied dysmenorrhea, she had documented endometriosis by a previous laparoscopy. We explained to her that endometriosis even without pelvic pain is generally positive for the inflammation marker known as BCL6 and is associated with considerably lower live delivered pregnancy rates despite IVF-ET [51,52].

It should be noted that her constipation and suffering was

very severe and was refractory to a gluten free diet and also did not respond to linaclotide. Her gastroenterologist had suggested a total colectomy and permanent ileostomy. With a dosage of dextroamphetamine sulfate of 37.5 mg her constipation was completely corrected with one painless bowel movement per day. She conceived after one treatment cycle of P and dextroamphetamine and delivered a full-term healthy baby. She continued with the amphetamine for 25 weeks of pregnancy but stopped it at the insistence of her obstetrician. Her constipation and severe abdominal pain resumed three weeks later. She started once again dextroamphetamine one month after delivery and her gastrointestinal issues completely reverted back to normal. She has had daily bowel movements and no abdominal pain for 1 ½ years postpartum.

Discussion

This case report presents some interesting observations and therapeutic options for treating patients who have infertility problems. First, consideration of the male factor as a cause of the infertility. The male partner in this case had a motile density of $3.2x10^6$ nl in his initial semen analysis. Considering both primary and secondary infertility, the couple had six years of infertility. Thus, with regular menses and patent fallopian tubes it would be reasonable to consider that oligoasthenozoospermia was a contributing factor, if not the only etiologic factor causing her primary infertility.

Though IVF-ET with ICSI would be one way to correct a male factor deficiency, so could IUI. In this case the motile density of the sperm, though subnormal, was not too low for conception by IUI (which negates the need for longevity of sperm staying alive in the cervical mucus). Nevertheless, achieving a pregnancy with natural intercourse was not out of the question if one could identify and correct an infertility problem with the female partner. One study found a 69% six-month pregnancy rate in couples where a female factor problem was identified and corrected e.g., LPD or anovulation, through natural intercourse in couples whose male partner had a motile density in the same range as this patient ≥2.5 to less than $5x10^6$ per ml [53]. In fact, there was a 22%, 6-month pregnancy rate with just intercourse when the motile density was less than 2.5 $10^{6/}$ nl [53].

This case also demonstrates that pregnancies are possible with sperm with subnormal motile densities even when there has been a progressive decrease in fertilization rates despite ICSI which was already low at 40% in the first cycle but had dropped to 18% in her last IVF-ICSI cycle. We only saw the female partner in person on the initial visit and monitored her by telehealth subsequently since they lived about 500 miles from our office. She sought an opinion from our fertility center that emphasizes methods to conceive naturally because she was financially depleted. It would have been interesting to evaluate a post-coital test as a method to determine how realistic the possibility of conceiving naturally could be [54]. Nevertheless, we were guardingly optimistic that this was possible in view of the fact that they did achieve chemical pregnancies without any treatment even after the last failed IVF cycle.

This case also provides insight into other aspects related to diagnosis and treatment of infertility. The female partner was found to have stage 1 endometriosis and the endometriotic lesions were ablated by laser. However, this did not result in a live delivery. An RCT performed by Nowroozi et al. published in 1987 evaluated the efficiency of removing stage I endometriosis by electrocoagulation in women who failed to conceive in eight months of all infertility factors corrected. All of these women did receive supplemental P in the luteal phase before the laparoscopy, during the preceding eight month and also thereafter [55].

Half the women were randomized to laparoscopic ablation of the endometriosis, if present, and the others were not given that option (at that time standard of care was not to surgically remove stage I endometriosis). The numbers were not exactly equal based on the fortuitous presence or absence of stage I endometriosis. The combination of endometriosis ablation and correction of ovulatory defects including P supplementation resulted in 61% of 69 women conceiving in eight months vs only 18% of 54 women where the endometriotic implants were not ablated [55]. Ten years later a large multicentered RCT by Marcoux et al. reached similar conclusions about the benefit of removing minimal or mild endometriosis [56]. However, two years later another large RCT failed to reach similar conclusions [57].

As a practicing physician, it becomes frustrating that in one given year a therapeutic modality seems to be effective based on an RCT, and thus convinces a physician to implement that type of treatment into one's own clinical practice repertoire, only to now have reservations based on a new RCT that reaches opposite conclusions. In that case, it behooves the clinicians to retrospectively evaluate their own data to see if there is validity of the therapy that those physicians are using. If their own data supports the RCT that finds no clinical benefit, it is important to determine if there are any differences in experimental design, e.g., in the case of ablating mild endometriosis, did both studies use P supplementation or not [58]. In the case reported here, perhaps had the patient received luteal phase P supplementation following the laparoscopic ablation maybe she would not have merely had chemical pregnancies but a live delivery [21].

There is evidence that endometriosis per se is not the cause of pelvic pain, but is actually caused by infiltration of irritating elements into the pelvic tissues causing inflammation, which, in turn, may cause infertility by immunological attack of the fetus by cellular immune cells [34]. It is not uncommon to find return of dysmenorrhea even in the very next time of menses following laparoscopic removal of endometriosis or just temporary relief. With the probability that removing endometriosis also does help some women to conceive, one hypothesis is that the endometrial implants exacerbate the permeability defect, and removing these implants, at least temporarily, decreases the excessive permeability. Evidence to support this is a study of second look laparoscopy two years later in teenage girls with severe dysmenorrhea whose implants were surgically extirpated. Though this procedure did, in fact, show the

absence of endometriosis in the large majority of these teenage girls two years later, half of them had the return of severe pelvic pain despite the absence of evidence of endometriosis [59].

Because women with pelvic pain with or without the documented presence of endometriosis have an increased frequency of diminished oocyte reserve (DOR), probably related to ovarian damage from chronic inflammation, if a medical option is present to decrease the excessive cellular permeability, that option may be a more suitable treatment protocol than laparoscopic ablation of endometriosis, which by its surgical nature could result in an even greater degree of DOR by directly damaging the ovarian tissue or the blood supply to the ovaries. Thus, one should choose the medical option not only because it may be superior to surgery to achieve a subsequent pregnancy, but avoids the risk of further depleting the oocyte reserve [60-64]. This is why our preference is to treat the patient with dopaminergic drugs, e.g., the dextroamphetamine taken by this patient, which better corrects the increased cellular permeability, and thus reduces excessive inflammation.

It is not uncommon to find the presence of mild or even stage IV endometriosis when performing a diagnostic laparoscopy for infertility investigation in women who deny any type of pelvic pain. It is becoming more appreciated that endometriosis can be associated with other medical conditions [41,43]. These pathological entities may be all related to this increase in cellular permeability which is not restricted to pelvic tissue [65]. In the case presented she had pathological constipation which was most likely the etiologic factor for her abdominal pain rather than endometriosis in view of the absence of any association with the time periods during the menstrual cycle that are typically associated with pain from endometriosis. Once the constipation was corrected, the pain dissipated. The laparoscopy failed to demonstrate any endometriotic implants on her bowel. This is the second case of complete correction of very severe long-term constipation with dextroamphetamine sulfate [50]. In the previous case, a teenage girl would never defecate in less than a nine-day interval and sometimes went six-eight weeks without a bowel movement. Her bowel movements became regular on a daily basis following treatment with dextroamphetamine similar to the patient described here. The constipation returned during times of drug shortage, only to be returned to normal once the medication was resumed. Thus, both of these women fulfilled Koch's postulates leaving little question that dopaminergic drugs can correct pathological constipation.

Recent concepts of what should be called a documented pregnancy is ultrasound confirmation of a gestational sac. Thus, it is not clear in view of the several chemical pregnancies achieved by the woman in this report whether her problem should be considered recurrent miscarriage or secondary infertility. For our purposes, we advised this patient that we considered that she was having recurrent early miscarriages. As previously mentioned, studies from the authors of this manuscript favor the beneficial effects of P in preventing miscarriage [20].

Nevertheless, the largest properly randomized evaluation of supplemental P to prevent miscarriage in women with which recurrent miscarriage known as the PROMISE study failed to find much benefit to preventing miscarriage by supplementing P [66]. The fact that it was published in one of the most prestigious journals (The New England Journal of Medicine) has led many obstetricians and gynecologists and infertility specialists to stop using P supplementation to prevent miscarriage. This PROMISE study did not change our opinion to use P to prevent miscarriage because the Coomarasamy et al. study was not properly designed. They added vaginal P as soon as the woman was diagnosed with a positive serum pregnancy test or within two weeks after the positive test [66]. The critical time to supplement the P is after ovulation to neutralize the killing effects of the cellular immune cells at the time of implantation and thereafter [67-69]. Subsequent to the Coomarasamy study Mary Stephenson again showed that taking supplemental P from early luteal phase and continuing it during the first trimester can reduce the risk of miscarriage [70].

The majority of our infertility patients come to us for a second opinion having failed to conceive with the treatment rendered by other infertility practices. We note that large percentages of these patients were never treated with progesterone or have been only given oral P supplementation which is usually insufficient because 90% is metabolized through first pass through the liver thus not gaining adequate endometrial concentration [20].

Though the majority of physicians are usually enamored by RCTs, sometimes, though, case reports e.g., the one presented, can influence a treating physician to consider a treatment (e.g., luteal phase P) in contrast to the conclusion of a large RCT, especially if a major flaw in experimental design can be pointed out, e.g., the timing and type of P supplementation. However, that physician should keep in mind to subsequently evaluate his/her own data to corroborate or refute the conclusion of the RTC as to whether that therapy is effective or not for their patient population. They should decide in their own mind, whether they should try supplemental P themselves even if they are generalists in obstetrics and gynecology, or to refer to an infertility specialist. If a referral to an infertility specialist is considered the best option for that patient, they should be aware of the normal fertility practices of that infertility center, e.g., whether the tendency of that infertility center is to advocate IVF-ET right from the beginning for infertility or IVF-ET and pre-implantation genetic diagnosis for recurrent miscarriage, and would that treatment be acceptable to their patient (e.g., not being affordable).

A physician accrues information from teaching rounds, lectures, books, and research publications, one of which may include meta-analyses, RCT's, case series, and case reports. All of these sources of information can help a treating physician to formulate a treatment plan. Hopefully this case report will make infertility specialists and generalists more aware of the option of using dopaminergic drugs for women with pelvic pain and suspected endometriosis rather than laparoscopy with its potential detrimental effect of

contributing to DOR [60-64].

Physicians should be encouraged to report in journals, or present at regional and/or international meeting their findings, pro or con, to promulgate this information to other physicians to hopefully provide new methods for treating refractory infertility or other medical conditions that are also treatment refractory.

As mentioned in the case reported here, we have continued her treatment with dextroamphetamine sulfate for 14 months postpartum. Unfortunately, many specialists in other fields refuse to continue with a drug that seems effective if it is off-label use. Thus, an OB-GYN or infertility specialist improving not only fecundity, but correcting some other pathological condition from which the patient is suffering by using dextroamphetamine, may have to continue their role as gastroenterologist, oncologist, rheumatologist, etc. because of witnessing, firsthand, the benefits of dopaminergic drugs for a variety of medical conditions. Dextroamphetamine sulfate is considered a class II drug. It is wrongly classified in our opinion since in the dosages used it has a very good safety profile, can be abruptly stopped without any withdrawal symptoms, and in the dosages used is very safe to the fetus. Thus, it can be continued not only during the first trimester to prevent miscarriage, but throughout the pregnancy to help treat other co-morbidities that would return if the amphetamine was stopped, as seen in the case described here.

There is another theoretical reason for continuing dextroamphetamine therapy is women with unexplained DOR even without symptoms of the increased cellular permeability syndrome. This woman had endometriosis without pelvic pain. The presence of endometriotic lesions in themselves is evidence of increased cellular permeability and inflammation even if pelvic pain is not present. Thus, it is not surprising that there is a greater likelihood of DOR when endometriosis is present [71-74].

Hopefully this case report will stimulate interest in other physicians treating infertility to consider the combination of dopaminergic drugs throughout the menstrual cycle and P in the luteal phase for women with infertility and report their findings to either corroborate or refute this concept of immune rejection of the fetal semi-allograft as an etiologic factor in diminished fecundity.

Finally, continuation of dopaminergic drugs may thwart the speed of subsequent follicle loss if subsequent pregnancies are contemplated. Certainly, dextroamphetamine or cabergoline would be preferred over surgical removal to treat pelvic pain because the surgery could markedly increase the rate of oocyte depletion [68-70].

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