Check JH, J Reprod Med Gynecol Obstet 2024, 9: 167
DOI: 10.24966/RMGO-2574/100167

HSOA Journal of
Reproductive Medicine, Gynecology & Obstetrics

Perspective

Treating Pelvic Pain and Endometriosis with the Goal of Correcting Infertility and/or Preventing Miscarriage

Check JH*

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Cooper Medical School of Rowan University, Camden, NJ, USA

Abstract

Though some women can achieve pregnancies despite various types of pelvic pain (mittelschmerz, dyspareunia, dysmenorrhea, vulvovaginitis, chronic pelvic pain, etc.), there is a higher frequency of infertility in the presence of pelvic pain disorders. Frequently, but not always, the pelvic pain is associated with the presence of either endometriosis or adenomyosis. As a physician it is imperative to develop a treatment protocol that would be the most effective with the least risk and the least cost. Though there is some place for laparoscopy and laser or excision type removal of endometriosis, this may cause harm by further compromising egg reserve. Since frequently pelvic pain equates to increased pelvic inflammation which can damage follicles and lead to diminished oocyte reserve, and even sometimes complete premature ovarian failure. Depending on the location of the endometriotic implants, surgical removal or damage to ovarian blood supply could further compromise egg reserve. Thus, our own philosophy is to correct all infertility factors first and treat with a dopaminergic drug, especially dextroamphetamine, but also bromocriptine or cabergoline. These drugs by releasing more dopamine from sympathetic nerve fibers will diminish excess cellular permeability in the luteal phase that leads to a greater infiltration of irritants into pelvic tissues that occurs in the luteal phase than the normal increase caused by progesterone inhibiting dopamine and thus leading to an influx of cellular immune white cells which aids in converting some thick walled uterine arteries into the thin walled spiral arteries which are needed for maternal fetal nutrient exchange. More investigation is needed to determine if additional use of antibiotics may be needed in some women to eradicate chronic endometritis which may contribute to the infertility-factor with pelvic pain.

Keywords: Dopamine; Dysmenorrhea; Endometritis; Fecundity; Increased cellular permeability

***Corresponding author:** Check JH, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Cooper Medical School of Rowan University, 7447 Old York Road, Melrose Park, PA 19027, USA, Tel: +1 2156354400; Fax: +1 2156352304; E-mail: laurie@ccivf.com

Citation: Check JH (2024) Treating Pelvic Pain and Endometriosis with the Goal of Correcting Infertility and/or Preventing Miscarriage. J Reprod Med Gynecol Obstet 9: 167.

Received: June 11, 2024; **Accepted:** June 19, 2024; **Published:** June 26, 2024

Introduction

I was recently invited to write a perspective for a journal on a subject of my choosing. I thus wrote the manuscript entitled "Most chronic medical conditions in women are related to increased cellular permeability" [1]. Based on this manuscript I was invited to submit a review or commentary related to this previous article by the Journal of Reproductive Medicine, Gynecology and Obstetrics. There are various goals for physicians, health care workers, scientists, and various types of employees of pharmaceutical companies who read scientific articles. Clinicians and healthcare workers may be looking to find more effective therapies, or additional treatments, to solve maladies for their consulting patients. Scientists may be looking for new ideas to help them to participate in understanding the nature of certain pathological entities which could then lead to new cures or at least significant palliation. Pharmaceutical companies may be seeking new ideas to create even more effective drugs to treat various conditions.

In this commentary/perspective I hope to present fodder for all types of readers. There are a multitude of publications, and so it is difficult for practicing physicians to develop their own treatment philosophy. Instead, they frequently rely on experts in their given field for guidance. However, when a given physician wants to provide their patients with the best advice and treatment, and thus turns to published manuscripts to help to establish a treatment philosophy for a certain condition, with the plethora of articles available to read on a given subject, frequently the physician will select as the best source of information a prospective Randomized Controlled Trial (RCT). Sometimes the last RCT published is the one that influences the treatment or new diagnostic criteria. Unfortunately, often times different RCTs performed in different centers frequently reach different conclusions. Then, generally a resident, fellow or new associate is given the task of performing a systematic review, and thus, with combining the data from all of the "proper" RCT studies, the goal is to provide the "correct answer" as to the efficacy of a given treatment modality, or a given diagnostic test, or criteria to guide the clinician to the right choices.

Unfortunately, depending on the criteria established by the author or authors, even meta-analyses performed at the same time frequently reach different conclusions. Sometimes subsequent to a given systematic review another large RCT which is consistent with the inclusion criteria, is subsequently published, which now completely changes the conclusion of the former meta-analysis. We are conditioned to believe that the most credible research presentation is a prospective RCT, followed by a prospective series type analysis with comparisons to historical controls, followed by a retrospective matched controlled

study, followed by a retrospective case series, and the last type of articles considered as most scientific value are case reports. Related to the great expense of RCTs, especially, the ultimate, which would be considered a multicenter RCT, most prospective RCTS are commissioned by pharmaceutical companies. These RCTS are generally needed for a given drug or diagnostic test to be approved by certain governing agencies, which would eventually lead to re-imbursement by third party insurance, thus rendering potential great profits. This tends to lead to certain biases, e.g., in patient selection, or even failure to publish negative data only publishing positive data. Unfortunately, many of the "experts" in a given field who are the teachers promulgating treatment guidelines are conducting many of these pharmaceutical clinical trials leading to financial gain by compensation for these studies, and thus they may be somewhat biased in their recommendations.

The aforementioned published article that showed that most chronic medical conditions in women (but men also) are related to increased cellular permeability referred mostly to case reports, some retrospective series, but no RCT's [1]. However, the large number of case reports treating women (and some men) with severe chronic disorders that were refractory to standard or even new experimental therapies, responding quickly, and effectively to dopaminergic drugs, especially dextroamphetamine sulfate, but also in a few cases to cabergoline, lends credibility of this concept not only by the large number of case reports on many different pathological entities, but also how severe their maladies were previously, yet now responding so well to dopaminergic drugs despite failure with conventional therapies. One of the functions of dopamine is to decreases cellular permeability, and the hypothesis was that excessive permeability leads to infiltration of irritants into different tissues and organs leading to inflammation with subsequent pain or organ dysfunction [2-4].

In the recent article that led to the request to write the article presented here we included published case reports and some case series, and the case reports sometimes referred to only one patient but sometimes several [1]. Some of the series included many patients e.g., the 50 with chronic fatigue syndrome refractory to all other therapies with 48 reporting marked improvement with dextroamphetamine and 2 stating the improvement was moderate [5]. One of the problems with a case report is that it may show that a given therapy may work (but possibly a fortuitous spontaneous remission) in one specific patient, but possibly most patients with that condition may fail to show response. This is not the case because I can state that usually there have been many other cases of that condition that have been successfully treated, and I have not changed my mind about the tremendous efficacy of dopaminergic therapy in the 45 years that we have used this treatment. For example, in my first published case of the beneficial effects of dopaminergic drugs dextroamphetamine treatment was given to 2 women with extremely severe treatment resistant chronic urticaria. They both responded extremely well, and this article was published 40 years ago in 1984 [6]. I can state for over 40 years we have treated many women with urticaria with some subsequent published case reports and case series and there has never been one of our patients who did not have a good response to dopaminergic therapy [7-9]. Even more important the patients do not become resistant to that therapy e.g., the 2 women reported 40 years ago are completely hive-free even today (except when on occasion they ran out of medication when the urticaria returns) [6].

In the recent article on the use of dopaminergic drugs to treat clinical healthcare issues in women there was a discussion about treating pelvic pain of various types with dopaminergic drugs [1]. However, there was not much discussion about its use for treating infertility. The commentary/perspective presented here will indeed include the beneficial aspects of dopaminergic drugs for treating infertility, but I will also be discussing other treatment protocols related to pelvic pain, endometriosis, and infertility other than dopaminergic drugs. However, I want to not only include my own treatment philosophy but recount other suggested therapies. The request was to write a "short" commentary. However, I look at requests to write articles as an opportunity for me to review recent literature to gain more insight about pain and infertility which could possibly alter to some degree my treatment philosophy going forward. Thus, I apologize this perspective will not be short.

Thus, for preparation in writing this commentary I read over 1,000 published abstracts and selected certain manuscripts for me to completely read. One of my ways to update my own education, and possibly change my treatment or diagnostic philosophy, occurs when I am writing new manuscripts. Before I elucidate the concept of inhibiting pelvic pain by decreasing cellular permeability with dopaminergic drugs, I hope to summarize, as briefly as possible, present concepts of treatment based on the reading of these articles and manuscripts. Many of these articles have over 200 references. Thus, I list the manuscripts that I read in case the reader wants to read more on the subject of conventional methods to treating pelvic pain and endometriosis with the objective of improving fecundity [9-58].

The creation of a working model of embryo implantation to provide some background for this concept of mechanisms involved in embryo implantation

I think it would be helpful to provide some background information about myself. My main medical interest initially was cancer immunology, and I was in a special program in both college and medical school where I did independent research and had grants from the National Cancer Institute. Thus, I completed a residency in internal medicine and was going to apply for a fellowship in oncology, hematology and immunology. My initial interest in research was to increase the exposure of some weaker antigens unique to the tumor but not to the adult human species, for the purpose of intensifying the antigenicity of these weaker cancer proteins to thus activate the cellular immune response and thus thwart cancer growth and spread by autologous vaccinations of killed tumor cells. Indeed, we were showing some success in inhibiting spontaneous murine cancers [59-62]. However, my thoughts were that this type of treatment would become costly and potentially valuable for a given patient with cancer, but not be ideal to treat a large volume of patients.

For a potential much wider application, I hypothesized that based on the similarity of the fetus and the malignant tumor, i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, that it would be likely that malignant tumors would similarly use mechanisms already in place to escape immune surveillance for the fetal semi-allograft. While conducting these murine cancer research studies, I initiated a human study to determine if radiation to the mediastinum, which would include the thymus in the field of radiation, may inhibit cellular immunity and potentially allow cancer to metastasize [63]. One of these human patients died from his stage IV non-Hodgkin's lymphoma and it became clear that I could not harden myself against human death. With a new medical field that was created, i.e., Reproductive Endocrinology and Infertility (REI),

thus bringing in life and happiness, rather than death, I decided to become an REI specialist not only to help infertile women or those with recurrent miscarriage, but to conduct research as to how the embryo/fetus escapes immune surveillance and then determine if cancer utilizes similar mechanism, Thus, my hope was to promote fecundity but thwart cancer.

After completing my fellowship in REI at Thomas Jefferson University School of Medicine I remained on the staff and eventually attained the position of assistant professor of medicine and associate professor of obstetrics gynecology. Subsequently I received a Ph.D. in reproductive biology and my thesis was "The role of progesterone in implantation fertility and inhibiting spontaneous abortion may be through the stimulation of immunomodulatory proteins" [64,65]. Eventually with a shift back toward cancer immunology, I was able to show that the production of the immunomodulatory protein, the Progesterone Induced Blocking Factor (PIBF), that requires membrane Progesterone up-Regulation (mPR) for its production, is the main factor allowing the large majority of all cancers to metastasize [66,67]. More importantly, we have demonstrated that PR antagonists can provide very significant palliation and considerable extension of lifespan even in end-stage very aggressive cancers with no more conventional or experimental treatment options [68,69]. For a more in-depth discussion of the PR's and cancer (nuclear and membrane) and immunomodulatory proteins e.g., PIBF and the Progesterone Receptor Membrane Component-1 proteins (PGRMC-1) the reader is referred to 3 additional reviews [70-72]. Thus, based on this working model of embryo/fetal implantation and cancer progression a novel highly effective treatment for advanced cancer has been found. With more research some hypothesized molecular events have been modified from the original model. However, the main importance of establishing a hypothetical model is to generate a novel potential treatment to help a pathological condition, and in this case, blocking the mPR seems to help the treatment of advanced cancer. As mentioned, on the flip side, at least in our own studies, the stimulation of these immunomodulatory proteins by supplementing P in the luteal phase has been highly effective in correcting infertility and preventing miscarriage [73-75].

The working model based on research studies over 30 years ago concerning the mechanism for embryo implantation, based on both clinical and molecular biology experimentation, suggested that though eventual suppression of cellular immune cells known to cause inflammation is critical during the luteal phase to allow embryo/fetal survival, it is just as important to initiate and enhance an inflammatory state in the early luteal phase to stimulate an autoimmune role in removing the thick walls of some of the uterine arteries to create thin walled spiral arteries to enable nutrient exchange between mother and fetus. Some of the research to date used to create this working model has been summarized [76-79]. The focus of this commentary/perspective is based on evidence that an exaggeration of the hypothesized mechanism to stimulate cellular immune cell invasion of normal tissue leads to excessive inflammation causing pain or organ dysfunction, not only in pelvic tissues, but throughout the body. Furthermore, this excessive inflammation may lead to diminished fecundity. I hypothesized that since the development of spiral arteries only occurred in the luteal phase, and shortly after P is secreted, it seemed likely that somehow P secretion enhanced an "invasion" of cellular immune cells. Since irritants provoke inflammation, I considered that P may inhibit a biogenic amine that normally works to decrease cellular and vascular permeability.

A publication in 1976 by Snider et al influenced my decision to consider dopamine as the likely biogenic amine that may be blocked leading to infiltration of irritants into various tissues leading to inflammation and frequently pain [80]. This article made me aware for the first time that Parkinson's disease, a condition of dopamine deficiency, is associated with sensory symptoms in various areas of the body. Apparently, the association of Parkinson's disease and pain symptoms had been known since 1921 and another subsequent publication occurred 40 years later in 1961 (and 15 years before the publication by Snider), also discussed various sensory pain symptoms associated with the disease of dopaminergic deficiency, i.e., Parkinson's disease [81,82]. In 1996 a published article by Ford et al demonstrated for the first time that pelvic pain in the form of vulvovagmils was not only frequently found in Parkinson's disease, but the pain markedly improved following treatment with levodopa [83]. Around the same time, there were 2 publications using rat tissue (unfortunately I could not locate them) that showed that dopamine diminished cellular permeability. Thus, I wanted to see if pain syndromes not associated with definitive dopamine deficiency, but relative inadequate dopamine response, may lead to increased cellular permeability, and consequential infiltration of various tissues with excessive irritants, and this in turn could cause various pain syndromes including, but not limited, to pelvic pain. To prove this hypothesis, I would need to demonstrate that taking a drug that releases more dopamine could thwart various pain or pruritis syndromes. I considered levodopa as having too many side effects. Thus, I wanted to use a drug with a greater safety profile. I found a study by David Streeten demonstrating that dextroamphetamine sulfate could inhibit the transudation of injected radio-active labeled albumen into women with cellular permeability defects by ingesting dextroamphetamine [84]. Subsequent studies did show that amphetamines do increase dopamine release [85].

Though we treated many women starting around 1980 with pelvic pain and other pain or pruritic conditions, my publications centered more on cancer immunology and the new developing field of in vitro fertilization embryo transfer. I could not find the time to also write case reports, which, though valuable, would not have the same scientific merit as larger powered studies. I thought when I had the time, I would write a large case series about the demonstrated clear beneficial effect of dextroamphetamine sulfate on pelvic pain and other pain syndromes. Though the hypothesis was that the pain relief was related to inhibiting excessive infiltration of irritants, it was also possible that the endometriosis implants themselves were mostly responsible for the pelvic pain or at least exacerbated the permeability defect. In fact, the permeability defect could be responsible for allowing menstrual tissue to escape. From about 1980 to 1984, we had successfully treated many women with dysmenorrhea and other types of pelvic pain with dextroamphetamine. In 1984 I was asked to present grand rounds and I presented this model of the mechanism of embryo implantation, and how based on this model one could develop many disorders related to increased cellular permeability with infiltration of tissues with unwanted irritants. Thus, treating with drugs that release more dopamine could possibly improve the symptoms of many pathologic disorders. An allergist in the audience after the lecture asked me if I ever treated urticaria with dextroamphetamine sulfate and I informed him that I had not. However, I thought it potentially could help chronic urticaria if it was related to irritants infusing into the dermis. He thus referred a woman covered in hives on most her body almost every day for 7 years who had not responded to any of the conventional therapies. The hives entirely disappeared within a few days after

treating with dextroamphetamine and she has been in remission now for 40 years (except when she ran out of medication 25 years later for months when they returned in a few days just as severe as before but disappeared again within 3 days after restarting the dextroamphetamine) [86]. This led to the referral of many patients with extra-pelvic pain syndromes. However, there were so many cases and many research studies ongoing at this time related to the new field of *In Vitro* Fertilization (IVF) and the cancer research, the next case report of the effectiveness of dopaminergic therapy was actually about a case of severe chest pain related to achalasia in 1990 referred to me by a fellow in gastroenterology who wanted to publish this interesting case [87]. Unfortunately, because other studies seemed more pressing, and non-IVF cycles are not computerized, I never got the opportunity to evaluate the efficacy of treating pelvic pain in improving pregnancy outcome or even determined the efficacy of this treatment for pelvic pain. However, I was aware that from experience at least 90% or more of patients treated with dextroamphetamine showed significant improvement in pelvic pain. Thus, I decided to write case reports on very convincing cases to share these treatment modalities with other physicians treating infertility and pelvic pain.

The first case report that I wrote on dopaminergic drugs to treat pelvic pain was published in 2005 and it concerned treating pelvic pain of bladder origin i.e., interstitial cystitis [88]. This captured the interest of one of our urogynecology fellows and we subsequently reported a small series of successes with this condition [89]. Our first case report of using sympathetic amine therapy for pelvic pain was reported in 2007 [90]. Subsequently, we published other case reports when there was something new that had not been reported before e.g. pelvic pain related to adenomyosis [91]. Subsequently, we demonstrated that pelvic pain may be associated with other pathological entities, and that these other conditions would also respond to dextroamphetamine along with the pelvic pain. Thus, we wrote some other case reports including dyspareunia also associated with interstitial cystitis and ocular migraines, or dysmenorrhea and chronic pelvic pain and mittelschmerz associated with Crohn's disease [92,93].

I presented this concept of etiology of pelvic pain at a conference in Dublin, Ireland. One of the attendees, Paul Carpentier decided to try dextroamphetamine on a number of women who did not respond to conventional therapy. He found that 68% of 75 women reported very significant pelvic pain relief after 3 months of therapy and overall 76%reported marked or moderate pain relief by 6 months [94]. Dr. Carpentier was not as aggressive with the dosage as in our practice but finally a series was presented, just not in our practice. However, this was even better, i.e., confirming the benefit of dopaminergic therapy for pelvic pain but in a separate practice [94].

The relative role of increased cellular permeability vs endometriosis in causing inflammation and pelvic pain, infertility, and miscarriage

The association of endometriosis and pelvic pain and chronic inflammation is well known [95]. One of the many questions to be answered was:

If one assumes that an increase in inflammatory cells above the normal amount to create spiral arteries, and thus causes chronic endometritis which may lead to infertility and recurrent pregnancy loss, then is the association of pelvic pain associated with reduced fecundity related to this chronic endometritis mechanism, or does the increased permeability leading to the escape of endometrial tissue cause infertility by the presence of ectopic endometrial tissue leading to the reduced fecundity in some other way? Women with endometriosis have been found to have an increased amount of inflammatory cytokines and inflammatory cells in the peripheral blood and in the endometrium and myometrium [96]. This is manifested by a large percentage of pro-inflammatory macrophages and uTH17/ T reg cell ratio favoring inflammation [96]. Similarly, with adenomyosis, there has been found an increase in proinflammatory cytokines e.g., Interleukin (IL) 6, ILlb, tumor necrosis alpha, and interferon gamma [22,97]. Other studies confirm a pro-inflammatory state with not only an increased presence of inflammatory cytokines, but also a decrease in regulatory T cells and dysfunction of uterine Natural Killer (uNK) cells [22,98,99].

Kitaya et al., discussed the fact that there are similar pro-inflammatory profiles in women with chronic endometritis and endometriosis but also some disparities [12,100]. Some women with endometriosis are quite fertile. Some women with extreme pelvic pain are not found to have endometriosis by laparoscopy nor have adenomyosis by imaging studies. There are still many questions to answer. I present next the 10 most important questions that I must consider in recommending a given treatment plan for women with infertility or a history of miscarriage and pelvic pain who are likely to have either endometriosis or adenomyosis.

- Does endometriosis/adenomyosis cause infertility related to frequently, but not always, causing implantation defects related to chronic endometritis?
- Does the increased cellular permeability defect leading to the increased inflammatory changes by causing a change in the microbiome, and thus is there a role for antibiotic therapy in improving fecundity in women with pelvic pain with or without the presence of endometriosis?
- If indeed bacterial infection is a factor in chronic inflammation what antibiotic therapy would be best to use to improve fertility?
- Would the use of dopaminergic drugs to reduce increased cellular permeability be sufficient to allow the body to restore a normal microbiome once the inflammation seems controlled as evidenced by eradication or marked improvement of pelvic pain? Alternatively, might it be necessary to treat with antibiotics to eradicate the predominance of new microorganisms even though this predominance occurred because of the increased cellular permeability which is now being corrected by treatment with dopaminergic drugs?
- Does the presence of endometriosis impair fertility in some other way than causing an adverse endometrium not conducive to successful implantation? For example, could endometriosis causing pelvic pain lead to infertility by having an adverse effect on embryo quality?
- If endometriosis may have an adverse effect on the endometrium and subsequent implantation, would correcting chronic endometritis by the use of dopaminergic drugs and the proper antibiotics be sufficient or will the presence of the endometriotic lesions still inhibit fertility, and if so, would surgically removing the endometriosis promote successful conception?

- Would the location of endometriosis without adhesions impair fertility in different ways? For example, would peritoneal implants be more prone to cause endometrial abnormalities with implantation failure whereas ovarian endometriosis could lead to egg quality issues? How does deep infiltrating endometriosis lead to reduced fecundity?
- What is the role of *In Vitro* Fertilization Embryo Transfer (IVF-ET) in treating infertility and pelvic pain related to endometriosis? Can natural conception be improved so that though taking a little extra time to conceive vs IVF-ET, would eventually be successful at a much lower cost?
- Is there a role for anti-estrogens or high dose progestin therapy for pelvic pain related to endometriosis for the purpose of improving conception?
- What role does Diminished Oocyte Reserve (DOR) (which is well known to be associated with endometriosis) play a role in the reduced fecundity? Furthermore, should the decision for therapy for pelvic pain (i.e., surgery or not) be influenced by the presence of DOR [101,102]?

The dilemma of how to treat women with pelvic pain and infertility with or without endometriosis

As mentioned, in the introduction, there are so many treatment options so that it becomes confusing for the clinician who wants to provide the best treatment option for his/her patient with the plethora of publications on this subject. Decision making may be compounded for many physicians by the presence of corporate medicine. Often physician groups can be quite large, and thus for many patients they do not have their care rendered by one physician but whoever is next available. This requires conformity of a treatment philosophy. Sometimes the "standard" practice for the group may not always be in the best interest of the patient, but instead the best financial interest for the medical group. In some countries, e.g., the United States, there are not that many private practices managed by one doctor or a very small group. This commentary/perspective is geared toward that minority group of physicians who want to provide the best and safest treatment options that are the most cost effective for the infertile women with pelvic pain and infertility.

One option for a therapeutic plan for a given clinician is to follow a model that makes sense to that clinician, (and then subsequently modify it to that clinician's own experience and patient population) is to follow the suggestions of a mentor that is experienced, but also has published his experience in peer-reviewed journals. If that mentor can also provide a new potentially more effective treatment than the ones presently used, then that is an extra bonus. However, initiating a treatment philosophy based on a trusted mentor is only a start. Subsequently that clinician must modify that treatment to adjust to their own patient population and their own financial needs to sustain a practice of medicine, and blend it with their own experience or philosophy from other mentors. I present my qualifications to allow the reader to decide how much of these suggestions would be worth incorporating into their present practice of medicine. I have been treating infertility for 50 years since completing my fellowship in reproductive endocrinology and infertility I have been involved in teaching medical students, residents, and fellows in reproductive endocrinology for 50 years with the first 15 years reaching the ranks of associate professor of OB-GYN, at Thomas Jefferson University School of Medicine where I completed my fellowship, and the last 35 years at Cooper Medical School of Rowan University (formerly Robert Wood Johnson Medical School). For the last 35 years until present my academic rank is full professor of OB-GYN and division head of reproductive endocrinology and infertility. My Ph.D. is in reproductive biology. I still work 50 hours per week in direct patient care. I have published over 800 peer-reviewed manuscripts in various journals and have published well over 1000 abstracts from meetings in which I participated. Probably, most important, when I left Jefferson to come to Cooper Medical School of Rowan University (formerly Robert Wood Johnson Medical School), I requested not to be paid by the medical school except an hourly rate for direct teaching so that I would maintain independence on decision making. I have never had more than 4 doctors in our group, and we are presently down to 2 infertility specialists, myself and Dr. Michael Sobel. Our philosophy is to choose the therapy that has the greatest potential to work taking into consideration risk to the patient or harm related to financial depletion. We are not afraid to "think outside the box." Finally, though I just turned 78 years of age, in my opinion senility has not yet set in (though you may disagree after reading this manuscript). Finally, we are in a geographical location where there are a great number of competing infertility specialists, and our hospital, Cooper Hospital, is an inner-city hospital in Camden, New Jersey with a lot of patients with New Jersey state insurance. Unfortunately, however, Medicaid does not reimburse the treating facility for infertility care. Thus, the practice is not sustained by direct feed by hospital referral and thus our maintenance of a very busy practice requires successful correction of infertility with subsequent referrals from satisfied patients which should provide the reader with at least some confidence in our suggested treatment philosophy.

Nevertheless, over the years we have modified our treatment philosophy based on our own research and others, so to do my due diligence in writing this perspective I read some recent articles to not only limit this perspective just to our own methods to treat pelvic pain and infertility,, but to add some potential modifications that we may employ going forward having been influenced by some of these other manuscripts [9-58]. I decided to present our present treatment philosophy taking into account the 10 nagging questions related to optimizing treatment of pelvic pain, endometriosis, and infertility possibly related to these pathological entities.

Treatment, philosophy based on the 10 questions: possible modifications based on new literature

Does endometriosis/adenomyosis cause infertility frequently, but not always, because of implantation defects related to chronic endometritis?

Logically, we would think that a treatment that markedly reduces pain without it being an analgesic, thus directed against excessive inflammation, should be an effective therapeutic agent to help correct infertility related to endometriosis. Thus, dopaminergic drugs, especially dextroamphetamine sulfate, would seem to be a logical treatment. From my latest literature search there is little if any data supporting that suppressing pain with other medical therapies i.e., estrogen suppression and/or progestins, improve fecundity. They have more side effects than dextroamphetamine and they have the distinct disadvantage of precluding pregnancy while they are being given. Thus, the delay in trying to conceive related to hormonal therapy increases the woman's age when she starts fertility treatment and leaves the possibility of further egg depletion.

There were no studies suggesting beneficial effects of general immunosuppressives e.g. glucocorticoids and/or immunotherapy. Furthermore, glucocorticoids have very significant immediate side effects and potential long term side effects as do immunosuppressives including very serious conditions e.g., developing cancer, or serious infections. Also, monoclonal antibody treatment is immensely expensive and would not likely be reimbursed by insurance carriers for off-label use. Finally, if one would attain significant immunosuppression, that could compound the infertility problem by inhibiting the increase in inflammation needed to remodel thick-walled uterine arteries to create thin-walled spiral arteries. Dopaminergic drugs, on the other hand are more likely to allow normal inflammatory changes but just inhibit an exaggerated inflammatory response that would be detrimental to fetal survival.

In our experience, we have seen many patients with long-term infertility and failure to achieve pregnancies, even with multiple IVF-ET cycles or continued miscarriages despite IVF-ET, have successes when dextroamphetamine was added [103]. We have recently submitted for possible presentation at the 2024 meeting of the American Society for Reproductive Medicine, a series of anecdotal cases where natural conception occurred after treatment of infertility with dextroamphetamine sulfate and luteal phase progesterone supplementation in women who previously failed to conceive despite a minimum of 3 IVF-ET cycles prior to their visit in our clinic (I cannot provide the data in case the abstract is accepted for presentation). B-cell lymphoma-6 (BCL6) is a master regulator of hormonal immunity and plays a key role in obstetric disorders e.g., pre-eclampsia [19,104]. Both mRNA for BCL6 and its protein are up regulated in the endometrium of women with endometriosis [105,106]. A high percentage of women with moderate to severe pelvic pain demonstrated the presence of endometriosis and upwards of 80% of women with endometriosis demonstrated elevated endometrial BCL6 in endometrial biopsies taken during the secretory phase [105,106]. Almquist et al., reported the results of 69 women having their 1st IVF-ET cycle for infertility without a tubal or male factor problem and thus considered unexplained infertility [107]. They found BCL6 to be positive in 52 of the 69 women with unexplained infertility having their very first IVF cycle. In the 17 women negative for BCL6 they had a live delivered pregnancy rate of 58% vs 11.5% in the 52 positive for the BCL6 marker [107].

We evaluated women having IVF-ET in our practice including male factor, tubal factor, and unexplained infertility who were not excluded for having previous IVF-ET cycles with failure to become pregnant. We treated those women with pelvic pain with dextroamphetamine sulfate titrating the dosage that best relieved the pain without causing side effects prior to performing IVF-ET and compared them to controls without pelvic pain and thus no dopaminergic drugs. Instead of finding a much lower pregnancy rate in those with pelvic pain (if one considers the results of the Almquist et al study) women < age 40 with pelvic pain taking dextroamphetamine had a slightly higher Live Delivered Pregnancy Rate (LDPR) than women without pelvic pain not taking dopaminergic drugs and the women > 40 with pain taking dextroamphetamine had a LDPR twice as high as those women >40 who had no significant pelvic pain and were not taking a dopaminergic therapy [78]. We have treated thousands of patients (mostly women but 5% males) with dextroamphetamine over the last 45 years, and so far, not one patient has developed addiction to the drug, no one was hospitalized for side effects from this sympathomimetic amine and no one has developed a long-term pathological complication from the drug e.g., osteoporosis as seen from glucocorticoids or estrogen suppression or even cancer from immunosuppressives. We usually continue through the first trimester, then abruptly stop the drug at the end of the first trimester or continue it throughout the pregnancy if a pathological entity is likely to return if one stops the medication e.g., headaches, inflammatory bowel disease, or autoimmune conditions [78]. The drug is safely administered to millions of children with attention deficit/hyperactivity disorder. Yet, for some strange reason it is considered a schedule II drug in the same category as fentanyl!

Our medical school and main infertility practice is in the state of New Jersey, but we have another clinic in Pennsylvania. For years, for unknown reasons, the state of New Jersey had a law precluding off-label use of schedule II drugs. There is no such law in Pennsylvania. Thus, New Jersey residents to receive a prescription had to be evaluated and seen in person at the Pennsylvania clinic. For some strange reason, the attorney general of New Jersey interpreted the law in such a way that he considered a patient and the doctor prescribing schedule II drugs, and in this case dextroamphetamine sulfate, which is an amphetamine, as breaking the law if the patient even brings the drug back into the state of New Jersey. One may think that the state of New Jersey is just very strict about drugs with potential abuse, and yet the state of New Jersey allows its constituents to acquire marijuana and "magic psychodelic mushrooms" at New Jersey state facilities without even consulting a physician! Before I capitulated to this state supported ban, I consulted a former attorney general of New Jersey and the attorney general of another state. They both said that in their opinion the state issued restriction was unconstitutional and I should legally try to fight the restriction. Unfortunately, I could not fight this odd interpretation for financial reasons. I mention this ban for several reasons. Some of you may want to try this medication after reading this commentary/ perspective but you may also find difficulties in writing the drug off-label. Thus, this new restriction gave me the impetus to try treating with another dopaminergic drug, cabergoline. I have found cabergoline to be effective to treat pelvic pain and other morbidities supporting the concept of the need to diminish excessive cellular permeability by releasing more dopamine [108,109]. Dextroamphetamine sulfate is a sympathomimetic amine, and the possibility exists that its efficacy worked in some other way than its effect on releasing more dopamine. The efficacy of cabergoline supports the contention that its main beneficial effect is in releasing dopamine.

A more credible way to convince fellow clinicians of the efficacy of dopaminergic therapy for pelvic pain and infertility is to compare cohorts of patients treated with dextroamphetamine sulfate vs untreated controls vs comparison to treatment with another drug e.g., cabergoline, to compare efficacy. This ban by New Jersey will eventually allow us to perform such a comparison because there is a significant number of New Jersey patients with pelvic pain and infertility not treated with any drug to inhibit increased cellular permeability, but just correcting other potential causes of infertility, and there are some who are taking cabergoline instead of dextroamphetamine. It will be important to run these comparisons both in natural and IVF-ET cycles. Our experience with correcting symptoms other than infertility from this increased cellular permeability syndrome is that cabergoline can work, but it also does not alleviate symptoms as well as dextroamphetamine sulfate. Usually, a dosage of 0.5 mg three times per week is required.

One should keep in mind that the increased cellular permeability syndrome can cause some clinical manifestation without pelvic pain, yet still lead to a hostile endometrium for implantation and thus cause infertility or miscarriage. We have recently reported 3 cases with long-term recurrent miscarriages or long-term infertility who had a live delivery following treatment with dextroamphetamine sulfate while enjoying marked improvement of their Crohn's disease, ulcerative colitis, or severe chronic constipation [110-112]. Because we believe so much in the benefits of dextroamphetamine therapy, and the seemingly greater efficacy for the various manifestation of the increased cellular permeability syndrome, ethical considerations prevent us from performing a prospective randomized controlled study. It will take at least another year to attain sufficient power to retrospectively compare dextroamphetamine vs cabergoline vs no pain therapy to determine efficacy for treating infertility in this manner.

Does the increased permeability defect lead to increased inflammation changes by causing a change into the microbiome? Thus, is there a role for antibiotic therapy improving fecundity in women with pelvic pain with or without the presence of endometriosis?

Lately there has been a greater interest among infertility specialists to consider chronic endometritis as diagnosed by an unusual infiltration of CD-138(+) plasmacytes in endometrial biopsies as a cause of unexplained infertility, recurrent miscarriage, multiple IVF-ET failures, and even some obstetric complications. To be honest, we have been so enamored with dopaminergic therapy that we assumed that the increased cellular permeability associated with endometriosis is the likely etiologic factor and that treatment with dextroamphetamine or cabergoline was sufficient. However, the publication by Kitaya and Yasuo has provided some food for thought [12]. Though they did find some commonalities between endometriosis and chronic endometritis, they also found some disparities [12]. We do sometimes perform endometrial biopsies and we do treat with 2 weeks of doxycycline if positive for endometritis, but I think from my re-evaluation of the literature that we do not perform this enough. Possibly the cellular permeability defect and the altered immune status make women with endometriosis more prone to chronic bacterial endometritis with common bacteria. One has to consider that chronic endometritis may be multifaceted and may occur in the absence of increased cellular permeability.

If indeed bacterial infection is a factor in chronic inflammation what antibiotic therapy would be best to use to improve fertility?

Antibiotic therapy including doxycycline, fluroquinolones and nitroimidazoles e.g., metronidazole or tinidazole have been shown to not only eradicate evidence of chronic endometritis but seemed to increase LDPRs following embryo transfer [113-116]. There are studies of failure to correct chronic endometritis despite standard antibiotic therapy. Lincomycin has been used to treat multiple drug resistant chronic endometritis in women with reported implantation failure [117].

Would the use of dopaminergic drugs to reduce increased cellular permeability be sufficient to allow the body to restore a normal microbiome once the inflammation seems controlled as evidenced by eradication or marked improvement of some pelvic pain, or alternatively, may it be necessary to treat with antibiotics to eradicate the predominance of new microorganisms even though the predominance occurred because of the increased cellular permeability?

One study found a higher success rate with live delivery when dydrogesterone was combined with antibiotic therapy [116]. Another study suggested superiority of combining GnRH agonists with antibiotics vs antibiotics alone [118]. This makes me consider that in some instances perhaps dopaminergic therapy plus antibiotics also may be ideal. Thus, I have decided to empirically add doxycycline treatment after 2 treatment failures with dopaminergic drugs to half of the patients (natural cycles or IVF) and give metronidazole to those patients who have failed to conceive after 3 cycles of dopaminergic drugs who were not treated with doxycycline in cycle 2. The haphazard way we perform endometrial biopsies for chronic endometritis with subsequent antibiotic therapy precludes me from gaining any meaningful retrospective data from our patient population. However, I will share one observation. Back in 1991, we published a study demonstrating a very low LDPR in pregnant women who despite fetal viability seen on ultrasound, if the sac had a gestational date more than 1 week earlier than what was determined by measuring crown rump length [119]. We considered that the loss could been related to infection with loss of amniotic fluid, and thus empirically treated these pregnant women with azithromycin. Anecdotally, we have experienced a high percentage of live deliveries since using antibiotics when we see a sac/crown rump discrepancy with small sacs, I plan to determine what is our success rate now, with antibiotic therapy and compare live delivery outcome to those with no sac discrepancies to determine retrospectively if adding antibiotics contribute to live birth and also is azithromycin the best choice of antibiotic taking into account risk to the fetus.

Does the presence of endometriosis impair fertility in some other way than causing an adverse endometrium not conducive to successful implantation? For example, could endometriosis causing pelvic pain lead to infertility by having an adverse effect on embryo quality?

There is some research to suggest that endometriosis may be associated with decreased oocyte quality [20]. The contention is that the quality issue is related to granulosa cell dysfunction related to inflammation and oxidative stress, aberrant steroid hormone production, and abnormal mitochondrial energy metabolism in those cells [20]. If, in fact, endometriosis is associated with decreased oocyte quality, one could theoretically improve fecundity by decreasing inflammation of granulocytes and improving mitochondrial dysfunction. Dextroamphetamine had been shown to markedly improve the chronic fatigue syndrome which has been linked to mitochondrial dysfunction [120-122]. Even more dramatically, treatment of a woman with the Mitochondrial Encephalopathy Lactic Acid Stroke like syndrome (MELAS), who was wheelchair ridden for 25 years was able to resume normal walking shortly after initiating treatment with dextroamphetamine [123]. This could suggest that since MELAS is a mitochondrial disorder, dopaminergic therapy may improve oocyte quality by improving mitochondrial DNA and then possible inhibit meiosis errors leading to aneuploidy.

Though I believe that endometriosis may to some degree negatively impair oocyte quality, I think the major impact is on implantation. We have a shared oocyte program where a woman receives a marked decrease in charges for IVF-ET, if she is willing to share half of her eggs collected with a recipient (who is the paying most of the bill) [124,125]. We compared during a 5-year period pregnancy rates in 24 recipients receiving donated eggs from donors with documented endometriosis by laparoscopy versus 144 women without endometriosis. The clinical and viable (past the 1st trimester) pregnancy rates for recipients of donor eggs from women with endometriosis were 42.9% and 38.1% and were 60.9% and 51.9% for recipients without endometriosis [126]. The implantation rates were 29.4% and 33.2% respectively. The small number of patients in the donor group with endometriosis precludes a statistical difference [126]. Nevertheless, one could look at this data as at least being consistent with endometriosis having a somewhat negative impact on oocyte quality possibly related to its damaging effect on granulocytes [20]. Other studies using sibling oocyte similarly reached the conclusion that endometriosis may have a negative effect on oocyte quality [127,128].

Unfortunately, our study was published about 20 years ago, and we cannot retrieve the data to determine how many of the 29 donors with endometriosis were also being treated with dextroamphetamine sulfate. Perhaps the LDPR in recipients of the egg donors with endometriosis may have been lower if the egg quality was not improved by the donor taking dextroamphetamine. Also, possibly donors with endometriosis had less eggs retrieved related to somewhat lower egg reserve thus contributing to a possible lower chance of live delivery compared to recipients without endometriosis.

If endometriosis may have an adverse effect on the endometrium and subsequent implantation, would despite correcting chronic endometritis by the use of dopaminergic drugs and proper antibiotics could the presence of the endometrial lesions still inhibit fertility, and if so, would removing the endometriosis promote successful conception?

Would the location of endometriosis without adhesions impair fertility in different ways? For example, would peritoneal implants be more prone to cause endometrial abnormalities with implantation failure whereas ovarian endometriosis could lead to egg quality issues? How does deep infiltrating endometriosis lead to reduced fecundity?

This commentary/perspective centers on the role of pelvic pain and infertility but in the presence of patent fallopian tubes and a normal tubal ovary anatomical relationship. The question here is whether or when should a laparoscopy be considered as a treatment modality with the thought of removing endometriosis to improve fecundity. Obviously if there are adhesions compromising tube-egg pick-up lysis should be performed, but what should be done about the presence of co-existing endometriotic lesions with or without the presence of adhesions? There is a plethora of published manuscripts both pro and con concerning the beneficial effect of laparoscopic removal of endometriotic lesions by laser vaporization or excision, and which of these procedures are superior taking into account the fertility aspect. So, to at least provide my opinion (which should not be taken as gospel). I consider our own research. We have a meticulous approach in attempting to achieve a pregnancy naturally before considering either a laparoscopy or IVF-ET [129]. Typically, the suggestion of either laparoscopy or IVF will not be provided initially by our team unless requested by the patients to have these procedures sooner.

In 1987, we published a study where women who had failed to conceive after a minimum of 8 treatment cycles where it was considered that all known infertility factors had been corrected, if we found mild peritoneal endometriosis on laparoscopy, one group was randomized to have the lesions ablated by electro coagulation then returned to the previous treatment that failed during the previous 8 months or more. The other group was given "the standard of care" at that time, i.e., we advised them that the laparoscopy just showed some mild endometriotic implants, but they should not be causing a problem with conception. They also resumed their previous infertility treatment. The LDPRs for the group with removal of endometriotic lesions were 60.8% of 69 women vs 18.5% of 54 women whose endometriosis was not removed [130]. Thus, for many years, and especially before the advent of IVF-ET, in our practice we suggested to women with pelvic pain and desire for having a pregnancy to undergo a laparoscopy if correction of other infertility factors still failed to allow conception. We were satisfied that the removal of the implants would be sufficient. Today, and for many years prior, our philosophy has changed, not because we doubt that removal of the implants would not improve fecundity, but that non-invasive dopaminergic drugs may be even more effective.

Today we generally advise laparoscopy in women with patent fallopian tubes by hysterosalpingogram who have failed after a reasonable number of documented or suspected causes of infertility (e.g., empiric treatment of women with supplemental progesterone in the luteal phase and dopaminergic drugs for those who have pelvic pain). If: 1) insurance reimburses for laparoscopy but IVF-ET is not re-imbursed. 2) The dopaminergic drugs have not been that effective in reducing pain sufficiently (which is uncommon) and the patient requests more pain relief without interfering with continued attempts to become pregnant. We are more reluctant to consider a laparoscopy in women with diminished oocyte reserve as evidenced by low serum anti-mullerian hormone levels or elevated day 3 serum FSH for fear of further compromising oocyte reserve. During a laparoscopy we are reluctant to laser or excise ovarian endometriosis or other endometriotic lesions whose removal may directly damage ovarian tissue or ovarian blood supply even in cases where oocyte reserve seems adequate.

What is the role of *in vitro* fertilization embryo transfer (IVF-ET) in treating infertility and pelvic pain related to endometriosis? Can natural conception be improved so that though taking a little extra time to conceive vs IVF-ET, would eventually be successful at a much lower cost?

My search of the literature did not provide new data that changed my usual philosophic approach. Thus, I will provide my usual way of deciding when or if to perform IVF in women with pelvic pain and infertility with the probability of endometriosis present. Though endometriosis can impair fertility in many ways, one of them may be related to the effect of endometriosis in causing diminished oocyte reserve [101]. It is well known that IVF-ET will provide higher pregnancy rates than non-IVF cycles. Sometimes IVF is used in my opinion too quickly by other centers. Sometimes I wonder if the main reason for success was not the IVF process per se, but the use of supplemental progesterone during the ET procedures. Many infertility practices are not as enamored as we are about progesterone supplementation in the luteal phase for natural cycles [129,131,132]. However, even in our own hands we generally find a 2.5-fold higher pregnancy rate in women with normal oocyte reserve or DOR

comparing natural to IVF-ET [133]. Even in our own hands where we give couples plenty of natural cycles to conceive and meticulously correct many potential infertility factors, and are aggressive with the use of dopaminergic drugs for pelvic pain and DOR without pelvic pain, we still found that IVF-ET results in a 2.5 fold increase in LDPRs vs natural cycles [129,133]. This illustrates the difficulty in making conclusions from other studies outside of one's own practice since protocols may be so different. One can only get ideas from these other studies or from commentaries/perspectives e.g., the one presented here, and then evaluate them in your own practice.

The discussion on when or if at all to use treatment with IVF-ET in women with pelvic pain and infertility but patent fallopian tubes and no significant male factor is ultimately up to the patient after hearing pros and cons. The patient needs to keep in mind that the presence of endometriosis could be more detrimental in time if it further impairs ovarian egg reserve if DOR is already present, or it could cause DOR if oocyte reserve is presently normal, and thus lower pregnancy rates somewhat even if the proper follicular stimulation protocol is used (which in my opinion is a protocol called the FSH receptor up regulation technique [134]. If the woman has had a recent laparoscopy and endometriosis was found and removed, but no tube/ovary impairment, she could consider to do IVF-ET to maximize her chances of conception because the beneficial effect of the surgery may be transient. However, based on insurance and financial issues, coupled with ethical and religious concerns, the couple could choose to resume natural cycles. Some women undergo the laparoscopy hoping to find correctable endometriosis or adhesions to hopefully allow techniques of correcting infertility naturally to now lead to a successful pregnancy despite previous failure.

If a person prefers to proceed directly with IVF-ET, I council them about the risk of pelvic pain and endometriosis on causing implantation failure and remind them that the process of IVF-ET will not correct the implantation defect. Thus, we generally advise them to try to conceive naturally while we titrate the dosage of dopaminergic drugs to alleviate the pelvic pain before proceeding to IVF-ET. Even in women with damaged fallopian tubes or severe male factor problem where IVF-ET is needed to achieve a pregnancy, we still recommend pre-treatment with dopaminergic drugs with continuation through the IVF-ET process and at least until completion of the first trimester.

Is there a role for anti-estrogens or high dose progestin therapy for pelvic pain related to endometriosis for the purpose of improving conception?

In reviewing the most recent literature there are no new studies to change my view that there is little convincing evidence that hormonal treatments for endometriosis can improve fecundity. Thus, I think that following surgical removal of endometriotic implants one should try to conceive as soon as possible taking advantage of possible transient improvement of fecundity following the surgical therapy rather than suppressing estrogen or adding progestins not to mention the possibility of side effect without benefit. On the other hand, there is a place for hormonal therapy in women not trying to conceive. My plan would be to try dopaminergic drugs first because by correcting the possible cause of the pain and presence of endometriosis the dopaminergic drugs may also impede egg depletion. Furthermore, they may be better tolerated. Nevertheless, an excellent discussion of hormonal treatments that presently exist for treating endometriosis and subsequent pain can be obtained by reading the article by Vannuccini et al., [10].

What role does Diminished Oocyte Reserve (DOR) (which is well known to be associated with endometriosis) play a role in the reduced fecundity? Furthermore, should the decision for therapy for pelvic pain be influenced by the presence of DOR [101,102]?

After acquainting myself with new literature that I had not read previously, I feel even more secure in my tenets and philosophy in dealing with DOR and pelvic pain with or without documented presence of endometriosis.

- Try to conceive as fast as possible even if there was hope to start a family later
- Consider oocyte cryopreservation if being pregnant is not feasible in the near future
- In view of possible diminished oocyte quality with endometriosis, and possibly that dopaminergic treatment may improve egg quality, consider pre-treatment for a few months with drugs e.g., dextroamphetamine before oocyte cryopreservation
- Natural conception is feasible and even if endometriosis is documented IVF-ET is not necessary. Though it may take 3 months to achieve a pregnancy vs one cycle of IVF-ET, natural conception is much less expensive
- Besides dopaminergic drugs supplemental progesterone in the luteal phase, especially vaginal or intramuscular, is essential, with careful attention to correcting follicular maturation defects, luteinized unruptured follicle syndrome or sperm/cervical mucus issues [129]
- Avoid surgery as best as possible, but if laparoscopy is performed, consider treating peritoneal implants less likely to deplete ovarian reserve and only treat ovarian or deep infiltrating endometriosis only when absolutely necessary
- If IVF is to be performed, consider a type of mild ovarian stimulation procedure known as the FSH receptor up regulation technique, if DOR exists [133,134]

Some of the world's most successful IVF centers have reported extremely low LDPRs, even with mild DOR when using conventional controlled ovarian hyperstimulation [135]. In contrast, when the principles of not increasing the serum FSH by anti-estrogen drugs or gonadotropins but just boosting with FSH when endogenous rise of estradiol has lowered the serum FSH, we find LDPRs in women with DOR to be only slightly reduced from their age peers with normal oocyte reserve [134,136]. As mentioned in the introduction, sometimes an exceptional case report can help support a hypothesis not proven but suspected. A 42-year-old woman with primary infertility was found to have DOR with a day 3 serum FSH of 47 mIU/nl. The only infertility factor found by sonography was that she failed to release the egg by follicular maturation studies. She failed to release 3 more times despite human chorionic gonadotropin injection of 10,000IU in cycle 2 and 15,000IU in cycle 3 and leuprolide acetate in cycle 4. Thus, besides DOR, she was diagnosed with the Luteinized Unruptured Follicle syndrome (LUF) [137]. She had been treated with dextroamphetamine after our 1st consultation related to pelvic pain and DOR. We tried a new therapy, a 100-microgram injection of Granulocyte Colony Stimulating Factor (G-CSF) the day before hCG injection. She released the egg by ultrasound and conceived on

her very 1st cycle of egg release, and delivered a healthy baby. She returned at age 46.5 in total menopause for about a year. She made a mature follicle on day 44 of her cycle after taking ethinyl estradiol to lower elevated serum FSH and restore sensitivity of the granulosa cells by up-regulating down regulated internalized FSH receptors. No gonadotropins were used consistent with the tenants of FSH receptor up regulation technique [133,138,139]. She developed a mature follicle on day 44, released the egg from the follicle and delivered another healthy full-term baby [140]. Anecdotally, we have observed a higher risk of LUF with ovarian endometriosis.

For the aforementioned case above possibly the use of dextroamphetamine improved egg quality and possibly endometrial receptivity. However, another case emphasized the dual potential role of dopaminergic drugs potentially impairing both egg quality, but in this case, very convincing evidence about improving endometrial receptivity. A 37-year-old woman with premature ovarian failure failed to conceive despite 4 fresh embryo transfers where the source of eggs were donated from younger women with normal egg reserve. The IVF center where she had the 4 fresh embryo transfers was known to have a high success rate in their donor egg program. They suggested using a gestational carrier because of a probable endometrial receptivity defect. However, both for financial reasons and her desire to at least have the experience of pregnancy and delivery, she consulted our practice. She was placed on dextroamphetamine, and we were planning to do another embryo transfer using fresh donor eggs. This usually takes a few months so to maintain proper endometrial tone we advised her to continue estrogen. We did suggest however, we could substitute oral estradiol with ethinyl estradiol so we can monitor her serum E2 in an attempt to make her ovulate and conceive naturally (though we thought that this was highly unlikely). She did in fact develop a mature follicle and she released the egg naturally and so we supplemented her with vaginal progesterone. She conceived that cycle and delivered a live baby [141].

Related to autoimmune factors possibly because of increased cellular permeability causing inflammation and damage to granulosa cells and the eggs in the follicles, we will frequently treat women with DOR without pelvic pain and even without other clinical manifestations of the increased cellular permeability syndrome with dopaminergic drugs as they are trying to conceive. Most women with DOR do not seem to have a history of factors that could have caused DOR e.g., pelvic surgery, radiotherapy or chemotherapy or even a family history of early menopause) Thus I suspect increased cellular permeability with ovarian damage related to infiltration of irritants causing inflammation and damage to the ovaries even with no symptoms or signs of the increased cellular permeability syndrome.

Conclusion

With the plethora of medical literature, it becomes a challenge to the clinicians in all areas of medicine to provide the best care and best treatment for their patients. Frequently "best treatment" suggestions are provided by an invited committee of experts. There is nothing wrong in following their guidelines. Unfortunately, some of the invited experts may have conducted clinical studies for large pharmaceutical companies, and thus some of their opinions could be somewhat jaded. One can learn from a single mentor with a lot of experience, but one must be sure that the suggested techniques are not outdated. Also, the words "in my experience" are insufficient unless the statement can be backed-up by statistics. I have tried to share my experience and thoughts to merely provide a starting point for the younger clinicians, and maybe alter to some degree the treatment philosophy of those more experienced in the field but yet open to hearing other suggestions. One should regard suggested therapies with caution. Thus if some of these policies are initiated, it is important to check your success rates because the type of patients representing the bulk of your practice could alter the benefit/ratio of a new treatment concept to one previously used. It is important if you believe that you have sufficient data publish your data corroborating or refuting some of these concepts. Hopefully, if nothing else, I have convinced you of the importance of publishing unique case reports that can influence treatment methodology by others.

Speaking of case reports, I should mention one last case. A 32 year old woman had never been able to insert a tampon nor have intercourse because of a severe problem of vaginismus type of genito-pelvic pain/penetration disorder. Part of her consult was to discuss future fertility (she wanted to try in about 1 year). She had failed to improve her vaginismus and dyspareunia despite many standard drug treatments and even pelvic floor physical therapy. She was able to have painless intercourse within one week of treatment with dextroamphetamine [142]. This dopaminergic drug may improve fecundity by allowing normal intercourse that was precluded by introital pain not to mention the beneficial effects on the woman's psyche and the stability of her future marriage.

Conflict of Interest

None.

References

1. Check JH (2024) Most chronic medical conditions in women are related to increased cellular permeability and most can be effectively treated with dopaminergic drugs. Biomed Res and Environmental Sci 5: 373-386.
2. Check JH, Katsoff D, Kaplan H, Liss J, Boimel P (2008) A disorder of sympathomimetic amines leading to increased vascular permeability may be the etiologic factor in various treatment refractory health problems in women. Med Hypothesis 700: 671-677.
3. Check JH, Cohen R, Katsoff B, Check D (2011) Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with sympathomimetic amines. Med Hypoth 77: 717-725.
4. Check JH (2017) Changing the name of a syndrome: Sympathetic neural hyperalgesia edema syndrome becomes-the increased cellular permeability syndrome. Clin Exp Obstet Gynecol 44: 819-823.
5. Check DL, Check JH, Katsoff B (2020) Dextroamphetamine sulfate therapy markedly improves the chronic fatigue syndrome. J Nurs Occup Health 2: 146-148.
6. Check JH, Gentlesk MJ, Falanga V (1984) Sympathomimetic amines in the treatment of chronic urticaria: Two reports. Cutis 34: 388-390.
7. Check JH, Amadi C, Kaplan H, Katsoff D (2006) The treatment of idiopathic edema, a cause of chronic pelvic pain in women: Effectively controlled chronic refractory urticarial-case reports. Clin Exp Obstet Gynecol 33: 183-184.
8. Check JH, Cohen R, Check D (2010) Idiopathic edema, a condition associated with pelvic pain and other symptoms in women, as a remedial cause of chronic cold induced urticaria. Clin Exp Obstet Gynecol 37: 235-236.
9. Check JH, Dougherty MP (2019) Use of sympathomimetic amines to correct premenstrual urticaria and anaphylaxis. Clin Exp Obstet Gynecol 46: 309-312.

10. Vannuccini S, Clemenza S, Rossi M, Felice P (2022) Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 23: 333-355.

11. Franasiak JM, Alecsandru D, Forman EJ, Gemmell LC, Goldberg JM, et al. (2021) A review of the pathophysiology of recurrent implantation failure. Fertil Steril 116: 1436-1448.

12. Kitaya K, Yasuo T (2023) Commonalities and disparities between endometriosis and chronic endometriosis: Therapeutic potential of novel antibiotic treatment strategy against ectopic endometrium. Int J Mol Sci 24: 2059.

13. Corachan A, Pellicer N, Pellicer A, Ferrero H (2021) Novel therapeutic targets to improve IVF outcomes in endometriosis patients: A review and future prospects. Hum Reprod Update 27: 923-972.

14. Shan J, Li DJ, Wang XQ (2023) Towards a better understanding of endometriosis-related infertility: A review on how endometriosis affects endometrial receptivity. Biomolecules 13: 430.

15. Szukiewicz D (2022) Epigenetic regulation and t-cell response in endometriosis-something other than autoimmunity. Front Immunol 13: 943839.

16. Pisarska MD, Chan JL, Lawrenson K, Gonzalez TL, Wang ET (2019) Genetics and epigenetics of infertility and treatments on outcome. J Clin Endocrinol Metab 104: 1873-1886.

17. Tan Z, Gong X, Wang CC, Zhang T, Huang J (2023) Diminished ovarian reserve in endometriosis: Insights from *in vitro*, in vivo, and human studies-a systematic review. Int J Mol Sci 24: 15967.

18. Giacomini E, Minetto S, Piani LL, Pagliardini L, Somigliana E, et al. (2021) Genetics and inflammation in endometriosis: Improving knowledge for development of new pharmacological strategies. Int J Mol Sci 22: 9033.

19. Louwen F, Kreis NN, Ritter A, Friemel A, Solback C, et al. (2022) BCL6, a key oncogene, in the placenta, pre-eclampsia and endometriosis. Hum Reprod Update 8: 890-909.

20. Fan W, Yuan Z, Li M, Zhang Y, Nan F (2023) Decreased oocyte quality in patients with endometriosis is closely related to abnormal granulosa cells. Endocrinol 14: 1226687.

21. Peitsidis P, Tsikouras P, Lagana AS, Laios A, Gkekes ID, et al. (2023) A systematic review of systematics reviews on the use of aromatase inhibitors for the treatment of endometriosis: The evidence to date. Drug Des Devel 17: 1329-1346.

22. Hoogstad-van EJ, Paap R, Nap A, van der MR (2022) The promises of natural killer cell therapy in endometriosis. Int J Mol Sci 23: 5539.

23. Csirzo A, Kovacs DP, Szabo A, Fehervari P, Janko A, et al. (2024) Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: A systematic review and meta-analysis. Surg Endosc 38: 529-539.

24. Arab W (2022) Diagnostic laparoscopy for unexplained subfertility: A comprehensive review. JBRA Assist Reprod 26: 145-152.

25. Huang N, Hongbin C, Qiao J (2020) Role of regulatory t cells in regulating fetal-maternal immune tolerance in healthy pregnancies and reproductive diseases. Front Immunol 11: 1023.

26. Lessey BA, Kim JJ (2017) Endometrial receptivity in eutopic endometrium of women with endometriosis it is affected, let me show you why. Fertil Steril 108: 19-27.

27. Sansone AM, Hisrich BV, Young RB, Abel WF, Bowens Z, et al. (2021) Evaluation of BCL6 and SIRT1 as non-invasive diagnostic markers of endometriosis. Curr Issues Mol Biol 43: 1350-1360.

28. Yoo JY, Kim TH, Fazleabas AT, Palomino WA, Ahn SH, et al. (2017) KRAS activation and over-expression of SIRT1/BCL6 contributes to the pathogenesis of endometriosis and progesterone resistance. Sci Rep 7: 6765.

29. Evans-Hoeker E, Lessey BA, Jeong JW, Savaris RF, Palomino WA, et al. (2016) Endometrial BCL6 overexpression in eutopic endometrium of women with endometriosis. Reprod Sci 23: 1234-1241.

30. Young SL (2024) Nonsurgical approaches to the diagnosis and evaluation of endometriosis. Fertil Steril 121: 140-144.

31. Klimczak AM, Herlihy NS, Scott CS, Hanson BM, Kim JG, et al. (2022) B-cell lymphoma 6 expression is not associated with live birth in normal responder *in vitro* fertilization population. Feril Steril 117: 351-358.

32. Nezhat C, Rambhatla A, Miranda-Silva C, Asiaii A, Nguyen K, et al. (2020) BCL-6 overexpression as a predictor for endometriosis in patients undergoing *in vitro* fertilization. JSLS 24: e2020.00064.

33. Ahn SH, Khalaj KK, Young SL, Lessey BA, Koti M, et al. (2016) Immune-inflammation gene signatures in endometriosis patients. Fertil Steril 106: 1420-1431.

34. Monsanto SP, Edwards AK, Zhou J, Nagarkatti P, Nagarkatti M, et al. (2016) Surgical removal of endometriotic lesions alters local and systemic proinflammatory cytokines in endometriosis patients. Fertil Steril 105: 968-977.

35. Rolla E (2019) Endometriosis: Advances and controversies in classification, pathogenesis, diagnosis, and treatment. [version 1; peer review: 4 approved] F1000Res 8: 1000.

36. Amro B, Aristondo MER, Alsuwaidi S, Almaamari B, Hakim Z, et al. (2022) New understanding of diagnosis, treatment, and prevention of endometriosis. Int J Environ Res Public Health 19: 6725.

37. Leyland N, Estes SJ, Lessey BA, Advincula AP, Taylor HS (2021) A clinician's guide to the treatment of endometriosis with elagolix. J Womens Health 30: 569-578.

38. Pirtea P, Cicinelli E, De Nola R, de Ziegler D, Ayoubi JM (2021) Endometrial causes of recurrent pregnancy losses: Endometriosis, adenomyosis, and chronic endometritis. Fertil Steril 115: 546-550.

39. Koninckx PR, Fernandes R, Ussia A, Schindler L, Wattiez A, et al. (2021) Pathogenesis based diagnosis and treatment of endometriosis. Front Endocrinol (Lausanne) 12: 745548.

40. Ahn SH, Edwards AK, Singh SS, Young SL, Lessey BA, et al. (2015) IL-17A contributes to the pathogenesis of endometriosis by triggering pro-inflammatory cytokines and angiogenic growth factors. J Immunol 195: 2591-2600.

41. Mitter VR, Meier S, Rau TT, Gillon T, Mueller MD, et al. (2021) Treatment following hysteroscopy and endometrial diagnostic biopsy increased the chance for live birth in women with chronic endometriosis. Am J Reprod Immunol 86: 13482.

42. McQueen DB, Maniar KP, Hutchinson A, Confino R, Bernardi L, et al. (2021) Redefining chronic endometritis: The importance of endometrial stromal changes. Fertil Steril 116: 855-861.

43. Herlihy NS, Klimczak AM, Titus S, Scott C, Hanson BM, et al. (2022) The role of endometrial staining for CD138 as a marker for chronic endometritis in predicting live birth. J Assist Reprod Genet 39: 473-479.

44. Liu Y, Phil M, Chen X, Huang J, Wang CC, et al. (2018) Comparison of the prevalence of chronic endometritis as determined by means of different diagnostic methods in women with and without reproductive failure. Fertil Steril. 109: 832-839.

45. Bonavina G, Taylor HS (2022) Endometriosis-associated infertility: From pathophysiology to tailored treatment. Front Endocrinol 13: 1020827.

46. Saunders PTK, Home AW (2021) Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell 184: 2807-2824.

47. Gruber TM, Mechsner S (2021) Pathogenesis of endometriosis: The origin of pain and subfertility. Cells 10: 1381.

48. Da Broi MG, Ferriani RA, Navarro PA (2019) Ethipathogenic mechanisms of endometriosis-related infertility. JBRA 23: 273-280.

49. Grammatis AL, Georgiou EX, Becker CM (2021) Pentooxifylline for the treatment of endometriosis-associated pain and infertility. Cochrane Database Syst Rev 8: CD007677.

50. Pasalic E, Tambuwala MM, Hromic-Jahjefendic A (2023) Endometriosis: Classification, pathophysiology, and treatment options. Pathol Res Pract 251: 154897.

51. Chen LH, Lo WC, Huand HY, Wu HM (2023) A lifelong impact of endometriosis: Pathophysiology and pharmacological treatment. Int J Mol Sci 24: 7503.

52. Clower L, Fleshman T, Geldenhuys WJ, Santanam N (2022) Targeting oxidative stress involved in endometriosis and its pain. Biomolecules 12: 1055.

53. Huang Q, Yu Y, Xu W, Li S, Zhou Y, et al. (2023) The role of peritoneal immunity in peritoneal endometriosis and related infertility. Front Biosci (Landmark Ed) 28: 166.

54. Somigliana E, Piani LL, Paffoni A, Salmeri NOM, Benaglia L, et al. (2023) Endometriosis and IVF treatment outcomes: Unpacking the process. Reprod Bio Endocrinol 21: 107.

55. Chang Y, Shen M, Wang S, Li X, Duan H (2022) Association of embryo transfer type with infertility in endometriosis: A systematic review and meta-analysis. J Assist Reprod Genet 39: 1033-1043.

56. Didziokaite G, Biliute G, Gudaite J, Kvedariene V (2023) Oxidative stress as a potential underlying cause of minimal and mild endometriosis-related infertility. Int J Mol Sci 24: 3809.

57. Carvalho Franca PR, Pereira Lontra AC, Dias Dernades P (2022) Endometriosis: A disease with few direct treatment options. Molecules 27: 4034.

58. Chen S, Liu Y, Zhong Z, Wei C, Liu Y, et al. (2023) Peritoneal immune microenvironment of endometriosis: Role and therapeutic perspectives. Front Immunol 14: 1134663.

59. Check JH, Childs TC, Brady LW, Derasse AR, Fuscaldo KE (1971) Protection against spontaneous mouse mammary adenocarcinoma by inoculation of heat treated syngeneic mammary tumor cells. Int J Cancer 7: 403-408.

60. Check JH, Brady LW, Leipold PL, O'Neill EA (1974) Protection against transplanted and spontaneous lymphoma by inoculation of heat-altered syngeneic tumor cells in splenectomized mice. Cancer 34: 197-203.

61. Check JH, Brady LW, O'Neill EA (1974) Differences in the protective effect of complete Freund's adjuvant in spontaneous versus transplanted lymphomas in AKR mice. Immunology of Cancer Tumor Res 19: 217-221.

62. Check JH, Silverman GA, Dryden RL, Brady LW (1979) Inhibition of spontaneous AKR Leukemia by multiple inoculations of corynebacterium parvum. Cancer 44: 488-491.

63. Check JH, Damsker JI, Brady LW, O'Neill EA (1973) Effect of radiation therapy on mumps delayed-type hypersensitivity reaction in lymphoma and carcinoma patients. Cancer 32: 580-584.

64. Check JH, Szekeres-Bartho J, O'Shaughnessy A (1996) Progesterone induced blocking factor seen in pregnancy lymphocytes soon after implantation. Am J Reprod Immunol 35: 277-280.

65. Check JH, Arwitz M, Gross J, Szekeres-Bartho J, Wu CH (1997) Evidence that the expression of progesterone-induced blocking factor by maternal T-lymphocytes is positively correlated with conception. Am J Reprod Immunol 38: 6-8.

66. Check JH, Nazari P, Goldberg J, Yuen W, Angotti D (2001) A model for potential tumor immunotherapy based on knowledge of immune mechanisms responsible for spontaneous abortion. Med Hypoth 57: 337-343.

67. Check JH, Check D (2019) Therapy aimed to suppress the production of the immunosuppressive protein progesterone induced blocking factor (PIBF) may provide palliation and/or increased longevity for patients with a variety of different advanced cancers-A review. Anticancer Res 39: 3365-3372.

68. Check JH, Check D, Srivastava MD, Poretta T, Aikins JK (2020) Treatment with mifepristone allows a patient with end-stage pancreatic cancer in hospice on a morphine drip to restore a decent quality of life. Anticancer Res 40: 6997-7001.

69. Check JH, Check DL, Poretta T, Srivastava M, Check E (2024) Significant palliative benefits following therapy with mifepristone for advanced treatment resistant small cell lung cancer. Anticancer Res 44: 659-664.

70. Check JH, Check DL (2021) A hypothetical model suggesting some possible ways that the progesterone receptor may be involved in cancer proliferation. Int J Mol Sci 22: 12351.

71. Check JH, Check DL (2023) The role of progesterone and the progesterone receptor in cancer: progress in the last 5 years. Exp Rev Endocrinol Metab 18: 5-18.

72. Check JH, Check D, Neumann B (2023) Future directions to explore to develop ideal anti-cancer progesterone receptor modulators. Cancer Sci Res 6: 1-8.

73. Check JH, Nowroozi K, Wu CH, Adelson HG, Lauer C (1988) Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. Int J Fertil 33: 252-256.

74. Check JH, Liss J, Check D (2019) The beneficial effect of luteal phase support on pregnancy rates in women with unexplained infertility. Clin Exp Obstet Gynecol 46: 447-449.

75. Check JH (2018) Pros and cons of the use of progesterone to reduce miscarriage rates. Clin Exp Obstet Gynecol 45: 652-655.

76. Check JH, Aly J, Chang E (2016) Improving the chance of successful implantation - part I - embryo attachment to the endometrium and adequate trophoblast invasion. Clin Exp Obstet Gynecol 43: 787-791.

77. Check JH, Aly J (2018) Improving the chance of successful implantation – part 2 – Circumventing immune rejection and the fetal semi-allograft. Clin Exp Obstet Gynecol 45: 9-13.

78. Check DL, Check JH (2020) Novel methods of improving fecundity and various pathological disorders based on a hypothetical model of embryo implantation. Gynecol Reprod Health 4: 1-15.

79. Check JH, Cohen R (2013) The role of progesterone and the progesterone receptor in human reproduction and cancer. Exp Rev Endocrinol Metab 8: 469-484.

80. Snider SR, Fahn S, Isgreen W, Cote LJ (1976) Primary sensory symptoms in parkinsonism. Neurology 26: 423-429.

81. Souques MA (1921) Des douleurs dans la paralysie agitante. Rev Neurol 1: 629-633.

82. Sigwald J, Solignac J (1960) Manifestations douloureuses de la maladie de parkinson et paresthesies provoquees par les neuroleeptigues. Sem Hop Paris 41: 2222-2225.

83. Ford B, Louis ED, Greene P, Fahn S (1996) Oral and genital pain syndromes in Parkinson's disease. Mov Disord 11: 421-426.

84. Streeten DHP (1978) Idiopathic edema: pathogenesis, clinical features, and treatment. Metabolism 27: 353-383.

85. Yorgason JT, Hedges DM, Obray JD, Jang EY, Bills KB, et al. (2020) Methamphetamine increases dopamine release in the nucleus accumbens through calcium-dependent processes. Psychopharmacology (Berl) 237: 1317-1330.

86. Check JH, Gentlesk MJ, Falanga V (1984) Sympathomimetic amines in the treatment of chronic urticaria: two case reports. Cutis 34: 388-390.

87. Leskowitz SC, Shanis BS, Check JH (1990) Resolution of atypical chest pain during treatment for idiopathic orthostatic edema. Am J Gastroenterol 85: 621-622.

88. Check JH, Katsoff B, Citerone T, Bonnes E (2005) A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin: case reports. Clin Exp Obstet Gynecol 32: 247-249.

89. Check JH, Cohen G, Cohen R, Dipietro J, Steinberg B (2013) Sympathomimetic amines effectively control pain for interstitial cystitis that had not responded to other therapies. Clin Exp Obstet Gynecol 40: 227-228.

90. Check JH, Wilson C (2007) Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines--case report. Clin Exp Obstet Gynecol 34: 55-56.

91. Check JH, Jaffe A (2015) Resolution of pelvic pain related to adenomyosis following treatment with dextroamphetamine sulfate. Clin Exp Obstet Gynecol 42: 671-672.

92. Check JH, Cohen R (2014) The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction. Clin Exp Obstet Gynecol 41: 575-577.

93. Check JH (2016) Increased tissue permeability and sympathetic nervous system hypofunction may be the common link between dysmenorrhea, chronic pelvic pain, Mittelschmerz, and Crohn's disease. Clin Exp Obstet Gynecol 43: 112-113.

94. Carpentier PA, Meier B, Check JH (2020) Sympathomimetic amine treatment very effective for relieving pelvic pain in women even when hormonal therapy and surgery were not sufficient. Fertil Steril 114: 203.

95. Vercellini P, Vigano P, Somifliana E, Fedele L (2014) Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 10: 261-275.

96. Vallve-Juanico J, Houshdaran S, Giuduce LC (2019) The endometrial immune environment of women with endometriosis. Hum Reprod Update 25: 564-591.

97. Bourden M, Santulli P, Jeljeli M, Vannuccine S, Marcellin L, et al. (2021) Immunological changes associated with adenomyosis: a systematic review. Hum Reprod Update 27: 108-129.

98. Tremellen KP, Russell P (2012) The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: adenomyosis and macrophages. J Reprod Immunol 93: 58-63.

99. Horton J, Sterrenburg M, Lane S, Maheshawri A, Li TC, et al. (2019) Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: A systematic review and meta-analysis. Hum Reprod Update 25: 592-632.

100. Kitaya K, Takeuchi T, Mizuta S, Matsubayashi H, Ishikawa T (2018) Endometritis: New time, new concepts. Fertil Steril 110: 344-350.

101. Check JH (2003) What role does decreased ovarian reserve play in the aetiology of infertility related to endometriosis? Hum Reprod 18: 653-654.

102. Seyhan A, Ata B, Uncu G (2015) The impact of endometriosis and its treatment on ovarian reserve. Semin Reprod Med 33: 422-428.

103. Check JH, Chern R, Katsoff B (2014) Prevention of first-trimester miscarriage with dextroamphetamine sulfate treatment in women with recurrent miscarriage following embryo transfer -- case report. Clin Exp Obstet Gynecol 40: 471-472.

104. Sitras V, Paulssen RH, Grønaas H, Leirvik J, Hanssen TA, et al. (2009) Differential placental gene expression in severe preeclampsia. Placenta 30: 424-433.

105. Lessey BA, Lebovic DI, Taylor RN (2013) Eutopic endometrium in women with endometriosis: ground zero for the study of implantation defects. Semin Reprod Med 31: 109-124.

106. Nezhat C, Rambhatla A, Miranda-Silva C, Asiaii A, Nguyen K, et al. (2020) BCL-6 overexpression as a predictor for endometriosis in patients undergoing *in vitro* fertilization. JSLS 24: 2020.00064.

107. Almquist LD, Likes CE, Stone B, Brown KR, Savaris R, et al. (2017) Endometrial BCL6 testing for the prediction of *in vitro* fertilization outcomes: A cohort study. Fertil Steril 108: 1063-1069.

108. Check JH, Check D (2023) Improvement of severe chronic pelvic pain and dysmenorrhea following treatment with cabergoline. Gynecol Reprod Health 7: 1-6.

109. Check JH, Check DL, Neumann B (2024) Marked improvement of severe treatment resistant migraine headaches with the dopaminergic frug cabergoline. J Med-Clin Res Rev 8:1-5.

110. Check JH, Check DL, Neumann B (2024) A novel treatment of Crohn's disease that is not only safe in pregnancy but can correct infertility and recurrent miscarriages. Gynecol Reprod Health 8: 1-9.

111. Check JH, Neumann B (2024) Combined dopaminergic drugs with supplemental progesterone to treat recurrent miscarriages and ulcerative colitis despite diminished egg reserve. Gynecol Reprod Health 8: 1-10.

112. Check JH, Neumann B (2024) Correction of treatment refractory infertility and severe constipation following treatment with supplemental progesterone and a dopaminergic drug. Gynecol Reprod Health (In press).

113. Kitaya K, Matsubayashi H, Takaya Y, Nishiyama R, Yamaguchi K, et al. (2017) Live birth rate following oral antibiotic treatment for chronic endometriosis in infertile women with repeated implantation failure. Am J Reprod Immunol 78: 12719.

114. Gay C, Hamdaoui N, Pauly V, Rojat HMC, Djemli A, et al. (2021) Impact of antibiotic treatment for chronic endometriosis or unexplained recurrent pregnancy loss. J Gynecol Obstet Hum Reprod 50: 102034.

115. Song D, He Y, Wang Y, Liu Z, Huang X, et al. (2021) Impact of antibiotic therapy on the rate of negative test results for chronic endometritis: A prospective randomized control trial. Fertil Steril 115: 1549-1556.

116. Qu D, Yang M, Tong L, Yu X, Jing Q, et al. (2021) Combination of dydrogesterone and antibiotic versus antibiotic alone for chronic endometritis: A randomized controlled trial study. Reprod Sci 28: 3073-3080.

117. Kitaya K, Ishikawa T (2022) Lincomycin administration against persistent multi-drug resistant chronic endometritis in infertile women with a history of repeated implantation failure. Appl Mirobiol 2: 554-560.

118. Khan KN, Fujishita A, Muto H, Masumoto H, Ogawa K, et al. (2021) Levoflaxacin or gonadotropin-releasing hormone agonist treatment decreases intrauterine microbial colonization in human endometriosis. Eur J Gynecol Reprod Biol 264: 103-116.

119. Nazari A, Check JH, Epstein R, Dietterich C, Farzanfar S (1991) Relationship of small-for-dates sac size to crown-rump length and spontaneous abortion in patients with a known date of ovulation. Obstet Gynecol 78: 369-373.

120. Check JH, Cohen R (2011) Sympathetic neural hyperalgesia edema syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue. Clin Exp Obstet Gynecol 38: 412-413.

121. Check DL, Check JH, Katsoff B (2020) Dextroamphetamine sulfate therapy markedly improves the chronic fatigue syndrome. J Nurs Occup Health 2: 146-148.

122. Check DL, Check JH, Citerone T, Cremin N (2020) Sympathomimetic amine therapy markedly improves severe fatigue that diminishes quality of life in patients with cancer-A case report. Cancer Sci Res 3: 1-3.

123. Potestio CP, Check JH, Mitchell-Williams J (2014) Improvement in symptoms of the syndrome of mitochondrial encephalopathy, lactic-acidosis, and stroke-like symptoms (MELAS) following treatment with sympathomimetic amines-possible implications for improving fecundity in women of advanced reproductive age. Clin Exp Obstet Gynecol 41: 343-345.

124. Check JH, Fox F, Choe JK, Krotec JW, Nazari A (2004) Sharing of oocytes from infertile versus paid donors results in similar pregnancy and implantation rates. Fertil Steril 81: 703-704.

125. Check JH, Wilson C, Jamison T, Choe JK, Cohen R (2012) The sharing of eggs by infertile women who are trying to conceive themselves with an egg recipient for financial advantages does not jeopardize the donor's chance of conceiving. Clin Exp Obstet Gynecol 39: 432-433.

126. Katsoff B, Check JH, Davies E, Wilson C (2006) Evaluation of the effect of endometriosis on oocyte quality and endometrial environment by comparison of donor and recipient outcomes following embryo transfer in a shared oocyte program. Clin Exp Obstet Gynecol 33: 201-202.

127. Shulman A, Frenkel Y, Dor J, Levran D, Shiff E, et al. (1999) The best donor. Hum Reprod Genet 14: 2493.

128. Simon C, Gutierrez A, Vidal A, Tarin JJ, Remohi J, et al. (1994) Outcome of patients with endometriosis in assisted reproduction: Results from in-vitro fertilization and oocyte donation. Hum Reprod 9: 725-729.

129. Check JH, Neumann B, Karnish AT (2024) Treating infertility without assisted reproduction techniques. Gynecol Reprod Health 8: 1-17.

130. Nowroozi K, Chase JS, Check JH, Wu CH (1987) The importance of laparoscopic coagulation of mild endometriosis in infertile women. Int J Fertil 32: 442-444.

131. Check JH, Nowroozi K, Wu CH, Adelson HG, Lauer C (1988) Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. Int J Fertil 33: 252-256.

132. Check JH, Liss J, Check D (2019) The beneficial effect of luteal phase support on pregnancy rates in women with unexplained infertility. Clin Exp Obstet Gynecol 46: 447-449.

133. Check JH, Choe JK (2022) Maximizing correction of infertility with moderate to marked diminished egg reserve in natural cycles by up-regulating follicle stimulating hormone receptors. Gynecol Reprod Health 6: 1-7.

134. Check JH (2022) A follicle stimulating hormone (FSH) receptor up-regulation technique as a method for follicular recruitment for *in vitro* fertilization-embryo transfer in women with diminished oocyte review. In: Berhardt LV (ed.). Advances in Medicine and Biology. Nova Science Publishers, Inc., Hauppauge, NY, .

135. Roberts JE, Spandorfer S, Fasouliotis SJ, Kashyap S, Rosenwaks Z (2005) Taking a basal follicle-stimulating hormone history is essential before initiating *in vitro* fertilization. Fertil Steril 83: 37-41.

136. Check JH, Wilson C (2013) The younger the patients the less adverse effect of diminished oocyte reserve on outcome following *in vitro* fertilization-embryo transfer as long as the proper ovarian stimulation protocol is used. J Reprod Contracep 24: 221-227.

137. Check JH, Dietterich C, Nowroozi K, Wu CH (1992) Comparison of various therapies for the luteinized unruptured follicle (LUF) syndrome. Int J Fertil 37: 33-40.

138. Check ML, Check JH, Choe JK, Berger GS (2002) Successful pregnancy in a 42-year-old woman with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and *in vitro* fertilization. Clin Exp Obstet Gynecol 29: 11-14.

139. Check JH (2010) The multiple uses of ethinyl estradiol for treating infertility. Clin Exp Obstet Gynecol 37: 249-251.

140. Check JH, Check DL, Richardson K (2022) Live delivery in a 46.5-year-old woman in overt menopause by restoring follicular sensitivity to follicle stimulation (FSH). Gynecol Reprod Health 6: 1-3.

141. Check JH, Katsoff B (2006) Successful pregnancy with spontaneous ovulation in a woman with apparent premature ovarian failure who failed to conceive despite four transfers of embryos derived from donated oocytes. Clin Exp Obstet Gynecol 33: 13-15.

142. Check JH, Check DL (2023) Eradication of long-term vaginismus type of genito-pelvic pain/penetration disorder by treating with dextroamphetamine sulfate. Gynecol Reprod Health 7: 1-5.

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752

Herald Scholarly Open Access, 2561 Cornelia Rd, #205, Herndon, VA 20171, USA.
Tel: +1 202-499-9679; E-mail: info@heraldsopenaccess.us
http://www.heraldopenaccess.us/