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A Novel Treatment of Crohn's Disease that is Not Only Safe in Pregnancy but Can Correct Infertility and Recurrent Miscarriages

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ABSTRACT

Rationale: *Treatment with dopaminergic drugs e.g., dextroamphetamine sulfate (DS) has provided marked relief of abdominal pain and diarrhea in patients with Crohn's disease who failed to respond to other therapies e.g., corticosteroids and biologic monoclonal antibody therapy directed against pro- inflammatory cytokines e.g., tumor necrosis factor-alpha treatment with DS has provided marked amelioration of Crohn's disease and dysmenorrhea thus relieving excessive bowel inflammation and pelvic inflammation with subsequent successful conception. The likely mechanism of action is through stimulating the release of dopamine from sympathetic nerve fibers leading to diminished cellular permeability thus limiting absorption of toxic elements into those tissues. There are reports of DS improving fecundity i.e. aiding conception and inhibiting miscarriage.*

Objective: *To see if DS combined with luteal phase progesterone in a woman with Crohn's disease but no pelvic pain suffering with infertility with diminished oocyte reserve can help her to conceive naturally despite failure with other therapies including in vitro fertilization.*

Findings: *Not only did the DS markedly ameliorate her inflammatory bowel symptoms but she also conceived naturally and has passed the first trimester with a live fetus.*

Conclusion: *At her last consultation with her previous fertility specialist, she was advised that she should proceed with donor oocytes. She probably had excessive endometrial inflammation despite the absence of dysmenorrhea. Thus, inflammation may have also caused damage to her ovarian egg supply. Dopaminergic drugs should be considered to help infertile women to conceive when there is evidence of other autoimmune disorders even with no apparent pelvic pain. DS is much safer to take during pregnancy than corticosteroids or biologics even with monoclonal antibodies especially in the last trimester.*

Keywords

Dextroamphetamine sulfate, Dopaminergic drugs, Increased cellular permeability syndrome, Inflammatory bowel disease, Spontaneous abortion.

Introduction

Some people are plagued by chronic abdominal pain, dyschezia, and diarrhea. This condition is termed inflammatory bowel disease. Though a subdivision of inflammatory bowel disease has been made e.g., Crohn's disease, ulcerative colitis, and microscopic colitis (both collagenous and lymphocytictypes) based on location, histologic changes, and colonoscopic evaluation and distribution of the disease, there can be a considerable overlap.

Crohn's disease is probably the most common presentation of inflammatory bowel disease [1]. Though contributing factors to the pathogenesis of Crohn's disease is probably multifactorial, one of the major factors is a polygenic (at least 100 genetic markers

have been identified) increased sensitivity of the intestinal mucosa to the bacteria of the gut, and is thus considered an autoimmune disorder [2,3]. Though, as mentioned, the distinction of the types of inflammatory bowel disease may be difficult, and there may be overlap, specific diagnosis may influence treatment. For example, amino salicylates e.g., mesalamine, may have efficacy for mild to moderate ulcerative colitis, but mesalamine does not seem to be effective for Crohn's disease [4]. There are various potential treatments for Crohn's disease, which sometimes are highly effective, but are frequently only mildly or moderately beneficial. Treatment paradigms have changed over the years related to continued controlled studies of the efficacy of previous standard therapies and the introduction of new treatments aimed to provide better efficacy and less potential serious side effects. The various agents that have been used (and are still in use by many practitioners even if therapeutic benefit is presently questioned), and newer agents, are divided into different types of therapeutic modalities. These include high dosages of 5-Amino salicylic acid e.g., mesalamine (despite recent failure to demonstrate superior efficacy to placebo), corticosteroids e.g. budesonide and prednisone [5]. It should be noted that present concepts of proper use of drugs for Crohn's disease is to only use corticosteroids for the initial induction phase of treatment to achieve symptom control, but not only have corticosteroids been found to not be very effective for maintenance treatment, but they are associated with significant risk of complications e.g., osteoporosis and risk of infection [5]. Some physicians prefer budesonide over prednisone because the former has reduced systemic absorption related to a high rate of metabolic clearances though first pass through the liver. Budesonide is less effective than prednisone, so the former is more often used in milder cases and prednisone in more severe cases [5].

Other treatments include immunosuppressive agents (thiopurines) e.g., azathioprine, 6 mercaptopurine, or methotrexate. These thiopurines have been found to be less effective thanbiologicals e.g. infliximab and some studies questioned their benefit over placebo [6-8]. Biological agents include drugs e.g., adalimumab, infliximab, certolizumab pegol, vedolizumab,and Ustekinumab. The biologics involve treatment with antibodies directed against molecules or cytokines required to produce the inflammatory process. One of the first targets was the pro- inflammatory cytokine tumor necrosis factor-alpha. The first TNF-alpha monoclonal antibody biologic was infliximab [9]. Initially, the TNF alpha inhibitors were only approved for patients with severe disease or those with less severe disease symptoms of Crohn's disease but who either had side effect from methotrexate, azathioprine, or 6-mercaptupurine, or these immunosuppressants were not producing significant improvement. Nevertheless, the TNF- alpha inhibitors over time were found not to be a panacea because 20-40% of patients to not respond at all to the anti-TNF-alpha biologics and an additional 23- 46% became refractory to these drugs over time [10]. One of the reasons for drug resistance to biologicswith monoclonal antibodies directed against TNF alpha is the development of antibodies by the human body against the biologic, which is also a protein. Though the usefulness of thiopurines has been questioned as to whether there is any solo benefit vs placebo in treating Crohn's disease, their main benefit seems to be to use then in combination with biologics directed against TNF alpha, which has been found to be more efficacious than the TNF alpha drugs alone [6]. One mechanism to explain this effect is that this combination seems to reduce the development of antibodies against these monoclonal antibodies than single use of biologics [6]. Once started, the recommendation is to maintain combined therapy for life because of a very high rate of recurrence if treatment is stopped.

Certain other molecules called interleukins may be required to promote inflammation. Thus, biologics against certain interleukins (ILS) e.g., Ustekinumab, which is directed against IL 12/23, has beendeveloped to treat Crohn's disease [11]. IL12 and IL23 help to promote the accumulation of inflammatory cells within the intestine [11]. Vedolizumab is a monoclonal antibody directed against alpha 4 beta integrin [12]. Thus, it prevents circulating immune cells from coming to the mucosa and is selective through interaction with mucosal adhesion molecules. Depending on the clinical status of the patient, the clinical remission rate ranged from 24-36% after induction therapy and the response rates ranged from 49-64% [12-16]. When used asa simple agent for induction of remission in mild cases, the average time to remission was 12-16 weeks, which was significantly longer than anti-TNF alpha drugs [12-16].

Patients with Crohn's disease have an increased risk of certain cancers. Chronic inflammation of the colon may result in an increased risk of colon cancer 2.5-fold and chronic inflammation of the small bowel inflammation may increase the much less common adenocarcinoma of the small bowel 31-fold [17]. For some reason the risk of melanoma is increased two-fold [18]. The risk of cancer is also increased by the standard medications. Using thiopurines increases the risk of melanoma two-fold and biologic treatments also increase the risk of melanomas two-fold [19].

The risk of lymphoma was increased two-fold with Crohn's disease treated by thiopurine and asimilar increased risk following single agent anti-TNF alpha drugs [20]. The risk of lymphoma was increased 6-fold by the common combined use of thiopurines and anti TNF alpha drugs [20]. There is a possibility that gut selective therapy with drugs e.g., vedolizumab may provide less risk of cancer, but this may be negated by less efficacy [21]. Patients with Crohn's disease have an increased risk of infection, especially pneumonia where the risk is two-fold higher even before treatment and double the risk of shingles. This inherent risk is considerably increased with corticosteroid therapy and mildly increased by monoclonal antibody therapy [22,23]. Anti-Crohn's therapy, especially this form, increases the risk of herpes zoster (shingles) [24]. Patients with Crohn's disease have an increased risk of clostridium difficile colitis when treated with antibiotics and this is increased in those receiving specific treatment for Crohn's [25]. There is another treatment for inflammatory bowel disease, including Crohn's disease, that has provided marked improvement of symptoms very quickly even in patients who did

not respond to standard therapy. This drug is dextroamphetamine sulfate [26-29]. In contrast to standard therapy for Crohn's disease, dextroamphetamine, in the pharmacological dosage used, poses no increased risk for cancer or infection, and has a much better safety profile than standard therapy.

Not only is dextroamphetamine sulfate safe, in general, compared to standard therapy but it is much safer for the fetus if needed to be taken during pregnancy [30-32]. Furthermore, it may even improve fecundity [33,34]. Thus, dextroamphetamine sulfate may be the chosen drug to be taken for Crohn's disease by women of reproductive age who are contemplating a pregnancy in the not-too- distant future. Dextroamphetamine sulfate is already in the pharmaceutical market and is widely used for treatment of attention deficit hyperactivity disorder (ADHD). Furthermore, it is available as a generic drug. Thus, it is highly unlikely that any pharmaceutical company would invest money to gain approval for re-purposing the drug for a new usage and, thus, it is unlikely that a randomized controlled study will be conducted to corroborate the findings of these case reports. Therefore it is important to continue publishing case reports of the use of dextroamphetamine for treatment of Crohn's disease and other inflammatory bowel disease disorders especially, as in the case described here, that illustrates another view of who are the best patients to treat with this amphetamine, i.e. woman with a history of infertility, recurrent miscarriage, or women of reproductive age who are contemplating pregnancy in the future.

Case Report

A woman at age 39 developed a gastrointestinal problem where she would have lower abdominal pain with eating or drinking that would last 30 minutes before it would gradually ease up. This was associated with 10-12 very loose bowel movements per day frequently associated with hematochezia. At age 40, she was diagnosed following colonoscopy and biopsy with Crohn's disease. She was initially treated with corticosteroids, and then treated with subsequently with single agent adalimumab 40mg per week. After a couple months the adalimumab did ameliorate her symptoms so that now her bowel movements were reduced to 5-6 times per day. Ther were still not formed but less watery, and hematochezia only happened rarely. The pain with eating now only lasted 20 minutes and the intensity was less, so it was now more bearable. Drinking no longer caused pain.

She continued on single agent adalimumab until age 41 when she decided she would like to become pregnant. Her gynecologist advised her that though there was limited human data about the adalimumab for the fetus so far, based on available data, it seemed reasonably safe. However, she was advised that the safety may be related to the monoclonal antibody not being able to the cross the placenta during the first two trimesters similar to immunoglobin G, but possibly it will cross the placenta and causes fetal harm when antibodies are known to be able to be transferred from mother to child in the last trimester.

Since she had primary infertility of two years duration, and she heard of our experience will women of advanced reproductive age and diminished oocyte reserve (DOR), (as evidenced by her serum anti-Mullerian hormone level of 0.572 ng/ml) she sought an opinion form our reproductive endocrinology/infertility practice. She had been to another infertility practice who advised her that her only option was to do *in vitro* fertilization (IVF-ET). She completed one cycle of IVF-ET with intracytoplasmic sperm injection but fertilized only one egg, and she failed to conceive after a day 3 embryo transfer. Her infertility specialist told her that she could only become pregnant using donor oocytes which was not an acceptable option to this couple. She was advised that based on anecdotal experience, dextroamphetamine sulfate will provide better symptom relief than adalimumab and at the same time improve her chance of a successful conception [27,28,33,34]. Furthermore, there has been much more experience with dextroamphetamine sulfate during pregnancy, and it has a very good safety profile for the fetus even with first trimester use [30-32].

She was started on amphetamine salts 15mg immediate release tablets AM and noon providing her with a dosage of dextroamphetamine sulfate of 18.8 mg per day. The dosage was gradually increased to a total dosage of 50mg amphetamine salts. She had no side effects with this dosage. She reported no longer any pain with eating. Her bowel movements were reduced in frequency to three per day, and even though soft, they were formed. There was no hematochezia.

Our assessment of her infertility problem was that it was related to advanced reproductive age, DOR and a mild to moderate male factor problem. The couple chose intrauterine insemination (IUI) rather than in vitro fertilization (IVF) with intracytoplasmic sperm injections (ICSI) for financial reasons. We informed them that the male factor issue was only mild, and that IVF would probably be a sufficient treatment. Her husband was not considered a candidate for medical treatment because his serum FSH level was top normal [35-37]. Since after her assessment of follicular maturation she attained the appropriate parameters for a more dominant follicle, she would not need any follicular maturation drugs. We strongly advised progesterone (P) vaginal suppositories 400mg 2x/day and oral micronized P once daily in the luteal phase and throughout the first trimester if she was successful with conception [38-40]. For ten cycles she made a mature follicle without any follicle maturing drugs, so she continued with no medication during the follicular phase other than the dextroamphetamine and metformin 1000mg 2x/day which she was taking for her type II diabetes mellitus. She conceived at age 42 on her tenth IUI cycle and the levels of human chorionic gonadotropin were rising appropriately, and fetal viability was established by pelvic ultrasound. She has completed the first trimester with a viable fetus.

We advised her to continue P after the first trimester, but she continues with the DS to delivery and while nursing rather than risk a flare of her Crohn's disease. Though the amphetamine can be detected in the nursing baby there does not appear to be any

detrimental effects on the baby [41,42].

Discussion

In general, the practice of medicine today more than ever before relies on "best" practice guidelines for treating various pathological entities. There may be more than one suggested treatment course which will be adapted by a given medical group which will be decided by the head of the group to follow. This is especially important for all physicians in these large groups to follow the same protocol so that physicians are interchangeable. With so many medications on the pharmaceutical market, and so many publications, with some having conflicting conclusions, many physicians look to some experts in the field to place complicated treatment options into a logical perspective. Indeed, Sulz et al. published a scholarly algorithm, not just for the general treatment of Crohn's disease, but algorithms for endoluminal Crohn's disease but also Crohn's with certain specific pathological associations e.g., an algorithm for treating Crohn's disease with fistulizing disease and algorithm for patients with Crohn's disease treated surgically to prophylactically prevent recurrent episodes [43]. This practical review was based on the guidelines ofthe European and Colitis Organization (ECCO) [44-46].

Almost aways are case reports are excluded from the systematic reviews and analyses, and quite frequently, these subspeciality experts' frown on off-label use of drugs. In our opinion, a treating physician should seriously consider in their approach to treating a given pathological disorder, a therapy that has a long-term safety record and good tolerance in many people (even if the use was for another condition), especially if that therapy, in certain case reports, produced much better efficacy than the standard therapy. This is especially valid if not only does the standard therapy have serious long-term risks e.g., the development of cancer or life-threatening infections, but also when the cost of treatment for the off-label drug e.g., dextroamphetamine sulfate, is only one thousandth the cost of one of the most common utilized standard drugs e.g., adalimumab.

One problem with a case report, rather than at least a series, is that the one physician reading the report is not cognizant as to whether the drug e.g., dextroamphetamine sulfate, may work, but possibly rarely. One does not know how often this treatment failed in other cases. The first case reportof using dextroamphetamine for treatment of Crohn's disease was published in 2010 [27]. Prior to the publication, the case was presented at a national inflammatory bowel disease meeting, along with another interesting case report of a patient with ulcerative colitis, who also responded very well to amphetamine therapy despite being refractory to standard therapy. This other case was published in the same journal as the case of Crohn's disease in 2011 [26]. When we subsequently submitted two other very interesting cases of another woman with severe treatment refractory Crohn's disease responding to dextroamphetamine sulfate and another woman with very severe microscopic colitis (30 bowel movements per day) who was reduced to one bowel movement per day following amphetamine therapy, these submissions were rejected for presentations at the meeting and were rejected from the journal Inflammatory Bowel Disease.

Eventually because of the association of inflammatory bowel disease and infertility and other gynecological disorders we subsequently published these cases with inflammatory bowel disease issuesin gynecological journals because of the association with infertility and pelvic pain [28,29]. The hypothesized mechanism considered that the common link between pelvic pain, inflammatory bowel disease, and other chronic pain disorder e.g., headaches and fibromyalgia and evenrheumatoid arthritis, is related to an increased cellular permeability of the tissues of a given organ leading to absorption of toxic elements into the tissues causing inflammation and pain [28,47,48]. The hypothesis suggested that pain was not the only manifestation of the syndrome, because absorption of elements into the mitochondria could lead to muscle disfunction resulting in chronic fatigue and even paresis [49-51].

Based on studying the mechanism of how the fetal semi-allograft escapes immune surveillance to determine if malignant tumors, even with weaker foreign antigens than the fetal-semi-allograft, could utilize similar mechanisms, we found evidence that an increased inflammatory response was needed during the luteal phase to bring in more cellular immune cells e.g., natural killer cells to remodel some thick-walled uterine arteries into thin walled spiral arteries to facilitate nutrient exchange between mother and fetus [52-56]. There is some suspicion that one mechanism to increase cellular immune cells, especially natural killer cells, was the action of progesterone in suppressing the biogenic amine dopamine. One of the functions of this biogenic amine is to diminish cellular permeability allowing irritants into pelvic tissues causing an inflammatory effect [48].

Based on these experiments and the hypothetical model that was formed it was reasonable that perhaps excessive inflammation could lead to various types of pelvic pain [28,33]. In view of the frequent transient benefit of surgical therapy for pelvic pain associated with endometriosis, we considered that the presence of endometriotic implants was not the cause of the pain but a result of the permeability defect allowing endometrial tissue in the menstrual fluid to escape into extrauterine positions. The hypothesis further suggests that the pelvic pain could possibly be ameliorated by treating with a drug that releases more dopamine from sympathetic nerve fibers [28]. Dextroamphetamine sulfate (DS) was chosen as the drug to try to improve various pelvic pain syndromes by releasing more dopamine from sympathetic nerve fibers. Indeed, it was found to be very effective for various types of pelvic pain [28,57-62]. Other drugs that release dopamine, but are not sympathomimetic amines, e.g., cabergoline may also relieve pelvic pain but perhaps, limited by side effects, our experience is that in general this drug is not as effective as DS [63].

It is well known that pelvic pain is usually worse at certain times of the menstrual cycle, which may be in part related to the

production of progesterone (P) which may further exacerbate the increased cellular permeability. Nevertheless, the possibility that other extra pelvic pain syndromes may be related to increased cellular permeability and absorption of toxic elements causing inflammation and thus they may also respond to dopaminergic drugs e.g.DS. Indeed, the first alimentary canal disorder associated with pain ameliorated by DS was achalasia [64]. There are several other gastrointestinal disorders that may be related to increased cellular permeability and responds to DS. Gastrocolic reflux syndrome may be associated with abdominal pain and diarrhea [65]. In contrast to diarrhea syndromes DS has helped pathological constipation [66]. Similar to the patient described in this case report, one tough longshoreman developed such severe abdominal pain after eating that he would be writhing on the floor in such severe pain after ingestion of food that would last 20-30 minutes, and he would vomit 25 times per day. His condition defied diagnosis despite evaluation by many gastrointestinal expert specialists from major university medical centers, until he received a diagnosis of mesenteric sclerosis diagnosed by a world-renowned medical center that had seen more than half of the reported 400 reported cases. He was advised that there is no treatment for this condition, and he will probably die within the year from a perforated bowel and sepsis. His condition completely disappeared after 1 month of DS [65].

Other serious gastrointestinal disorders may be associated with substances permeating gastrointestinal smooth muscle and may cause muscle dysfunction e.g., gastroparesis and pseudo intestinal obstruction which all responded extremely well to DS despite being very refractory to standard therapy [67-69]. The patient with pseudo intestinal obstruction deserves some mention not published in her case report [69]. She had some abdominal pain, but stopped growing, lost weight (was in the 3rd percentile of weight) and was diagnosed by colonoscopy as having Crohn's disease. She seemed to respond to sulfasalazine after a few months. She eventually switched to mesalamine and continued to do well until age 21 when she developed post- prandial abdominal pain and early satiety and lost weight from 110 pounds down to 75 pounds. Repeat colonoscopy showed no evidence of Crohn's but eventually tests showed that she had pseudo intestinal obstruction for which there was no standard treatment. However, she responded very well to treatment with dextroamphetamine sulfate and regained her weight. Though usually most conditions treated by DS resume when treatment is stopped, after several years she tried stopping DS, and her symptoms have not returned in the last 15 years. Perhaps she was misdiagnosed at age 5 and had pseudo intestinal obstruction at that time and either she had eventually a spontaneous remission or perhaps mesalamine may be ineffective for Crohn's disease but may help pseudo intestinal obstruction. The main point we are trying to make it is that whereas distinction between ulcerative colitis and Crohn's disease may be important in deciding on a therapeutic approach (e.g., mesalamine or not) it does not seem to matter what is the final type of clinical symptoms and signs or physiological or histological differences, in patients with abdominal pain, it seems that most cases of gastrointestinal manifestations of the increased cellular permeability syndrome respond well to DS.

Over a 20-year time period we have seen over 30 cases of abdominal pain without chronic pelvicpain or menses associated pain, with at least 10 cases of Crohn's disease, and all have had good response to DS despite unsatisfactory results from other treatments. The case reported here was not the worst case we have ever seen with good response, but we describe her because of the possibility that her Crohn's disease, without typical pelvic pain, may contribute to infertility. This autoimmune condition may have played a role in her DOR, but possibly also in autoimmune attack of the fetal semi- allograft. Though it cannot be proven for sure, but possibly the use of DS may have helped her to achieve the pregnancy despite her advanced reproductive age and DOR. We discuss this case for another reason, and that is to share our philosophy about treating infertility, in general, and specifically in women with advanced reproductive age, with or without DOR. Her previous infertility specialist immediately recommended IVF even though she could not afford it. Wecould argue that IVF-ET with ICSI for advanced female age and oligospermia in her male partner would give her the best chance of conceiving per cycle. However, she spent a lot of money for the one failed cycle. She was told by that fertility specialist that her chance of conceiving with another IVF-ET cycle would be less than 1% and tried to convince her that donor eggs were her only realistic option. Obviously, that was not true. Though it took ten cycles of IUI's, which were covered by her insurance company, she did not have to become financially depleted to achieve her dream of having a baby withboth her and her husband's genes.

We obviously cannot say for sure that progesterone (P) supplementation alone without DS may have also achieved success. Some physicians do not even believe that luteal phase P supplementation can correct infertility problems and would say that miracles just sometimes happen. Nevertheless, our data support the concept that P alone in the luteal phase may be a highly effective treatment of infertility [70-72]. We reasoned that even if the DS was not necessary for her achieving this pregnancy, there was a good chance it would markedly improve her symptomatology for Crohn's disease. We could have agreed to perform IVF-ET if that was what the patient desired because it would have increased her chance of conception 2-3-fold per cycle. However, we would have not used high dosage gonadotrophins to stimulate her follicular or maturation (infertility specialists typically use higher dosages of gonadotropins for DOR hoping to make more eggs) because we have data suggesting the increase in serum FSH may markedly diminish the chance of a successful pregnancy [73]. Instead, we would have used a type of mild form of ovarian stimulation referred to as an FSH receptor upregulation technique [74,75].

We recently submitted for publication a case of a 37-year-old woman without pelvic pain but suffering from ulcerative colitis who did not respond well to standard therapy but who not only had complete abrogation of her gastrointestinal symptoms with DS,

but also conceived and delivered a healthy full-term baby after just one cycle of P support in the luteal phase, and with just intercourse. She continues on DS post-partum and continues to do well now one year later. Her previous infertility specialist told her that her only treatment option was to use donor eggs.

Interestingly another woman presented at age 42 with DOR but wanted to conceive naturally.

We found she did not release her egg from the dominant follicle [76]. On her fifth natural cycle (she made dominant follicles despite a day 3 serum FSH of 47 MIU/ml) following a new treatment for the luteinized unruptured follicle syndrome (the use of granulocyte colony stimulating factor) with natural intercourse but also with DS and P supplementation, she had a successful conception in this first cycle ofegg release [77,78]. The women returned at age 46.5 in total menopause and wanted to conceive againand this time we used ethinyl estradiol to restore down regulated FSH receptors [74]. We also gave her granulocyte colony stimulating factor and human chorionic gonadotropin when her follicle achieved maturity criteria on day 44 [77]. She released the egg and delivered a full-term healthy baby [79]. She did not have any symptoms of the increased cellular permeability syndrome other than DOR.

Though the case we describe in this manuscript did not have the worst case of Crohn's disease that we have successfully treated with DS, we described her case to also show that perseverance may be important with her taking ten cycles to conceive (not just the first cycle as described some of the other cases mentioned). The case presented in this manuscript and the other cases of advanced age and/or DOR have several things in common related to consultations with different infertility specialists. All reproductive endocrinologists tried to direct them toward donor eggs, but if they were willing to try IVF-ET their infertility specialists insisted on pre-implantation genetic testing before transferring any embryos. None of the infertility specialists were willing to try to help them conceive without either IVF or donor oocytes. We could not understand what was the rush toward donor eggs. There is no time limit for usingdonor oocytes since pregnancy rates using younger donor eggs in women in their late 40's are the same as women in their late 20's [80]. Women in their 40's are much less likely to get pregnant with IVF than younger women so why make them spend so much money if insurance does not pay for the procedure (even though the pregnancy rate per cycle is higher) especially when there is no absolute reason whyIVF is needed e.g., blocked fallopian tubes, or very severe male factor problems.

One final point of discussion that was not presented in this case report. The other woman mentioned with severe Crohn's disease after forming a relationship with a male partner decided to get pregnant at age 42 [27]. She had DOR and a short follicular phase, so she was treated with ethinyl estradiol to lengthen the follicular phase and used P supplementation in the luteal phase and continued her DS [81]. She conceived after 2 cycles after completing the first trimester, so we discharged her to herobstetrician from the hospital of a major medical school. We had advised her to remain on the DS for fear of recurrence of her Crohn's disease. She was referred to maternal/fetal medicine at the same university medical center who advised her to stop the DS because auto immune disorders usually go into remission during pregnancy. She stopped the DS without our knowledge to advise her with our opinion. Shortly thereafter, all of her diarrhea and abdominal pain returned. She was referred back to her gastroenterologist from the same university medical center. They advised her to have a partial bowel resection and temporary ileostomy until the completion of the pregnancy and for eight months post- partum when they would re-anastomose the colon. They were hoping that the bowel rest with the continuation of adalimumab would heal the colon. They completely ignored the fact that she did not want to have the surgery in the first place and that's why she consulted us and did so well with DS treatment. They ignored how well she felt on DS because that was not one of their treatment protocols. Surprisingly, she agreed to the surgery.

The baby was healthy at birth. She had the re-anastomosis eight months post-partum. Unfortunately, all of her symptoms returned. Her gastroenterologist team advised total colectomy. She refused and came back for treatment with DS. She has been asymptomatic for several years while takingDS. The point to be made from this case of the woman who did undergo the partial bowel reconstruction that if the gynecologist or infertility specialist treats a woman with inflammatory bowel disease who is also trying to conceive, they should be aware that they should be prepared to be the physician who continues the DS not only during the entire pregnancy but also post-partum. There was a 2014 prospective cohort study performed in women with various autoimmune disorders for which they were prescribed anti-TNF alpha drugs including infliximab, adalimumab, or etanercept in the first trimester [82]. Miscarriages occurred in 10.8% vs 5.8% in disease-matched controls not taking these drugs [82]. Pre-term births occurred in 20.7% of women taking TNF alpha suppressors vs 14.3% of disease matched controls. Birth weight was also lower in the TNF-alpha group (2975 vs 31599ms) [82]. Thus, though there was no evidence of an increase in congenital malformation, both TNF alpha groups and non-treated patients with autoimmune disorders had more adverse pregnancy outcomes than controls without autoimmune disorders.

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