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Review Article

Treating Dysmenorrhea with Dopamine Agonists has the Advantage of Ameliorating other Clinical Pathologic Entities that are Frequently Present at the same time

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Abstract

There is evidence to support the concept that the development of thin-walled spiral arteries during the luteal phase and throughout pregnancy is needed for nutrient exchange between mother and fetus may be more from autoimmune remodeling of the thick-wall uterine arteries found in the proliferative phase rather than neovascularization. One of the functions of dopamine is to decrease cellular permeability. Research supports one mechanism to stimulate a cellular immune response during the luteal phase to achieve autoimmune stripping off of the thick cellular walls of uterine arteries is by progesterone blocking the effect of dopamine allowing irritants to cross the mucosal barrier into pelvic tissues. Evidence supports that normal inflammatory state in the luteal phases is not associated with significant pelvic pain. However, excessive permeability leading to excessive infiltration of irritants may lead to severe pelvic pain of various types and possibly allow escape of endometrial cells which subsequently may implant and proliferate in ectopic places, resulting in endometriosis. The relative increase in permeability may be related to infiltration of irritants into the pelvic tissue from injury, infection, etc., or may be related to a relative dopamine deficiency. In the latter circumstance, there may be other tissues that are more permeable, and therefore subject to extra inflammation and pain or organ dysfunction either all the time or exacerbated during the luteal phase. A case is presented with not only pelvic pain, but several other pathological entities. Not only did the use of the dopamine agonist dextroamphetamine eradicate the pelvic pain, but also other of her other comorbidities. Thus, dopamine agonist therapy has the advantage over all other types of medical or surgical therapy for pelvic pain with or without the presence of endometriosis in that it allows, and possibly aids women to achieve pregnancies or prevent miscarriage while at the same time ameliorating several other comorbidities frequently found in conjunction with pelvic pain.

Keywords: Dysmenorrhea; Increased Cellular Permeability Syndrome; Dopamine Agonists; Infertility; Progesterone

Introduction

There is evidence that an essential step in the process of successful embryo implantation is to create arteries with a cell wall that is only 1 cell thick; i.e., spiral arteries, to allow nutrient exchange between mother and fetus [1]. These spiral arteries appear during the luteal phase. There are two possible ways that these spiral arteries could be created: neovascularization or remodeling of some of the thick-walled uterine arteries found during the follicular phase [1].

Neovascularization would require a genomic mechanism that would involve the nucleus. Since these vessels form shortly after the increase in progesterone secretion, neovascularization could theoretically be related to the interaction of P with nuclear

P receptor (nPRs). However, genomic mechanisms are generally slow processes, and although neovascularization could account for some of the spiral arteries, they appear too quickly to have neovascularization as the main mechanism. The interaction with membrane PRs (mPRs), which produce much quicker responses, would seem to be a more logical mechanism to explain spiral artery creation. [2,3].

Related to the speed of spiral artery formation, this would favor the remodeling hypothetical mechanism, and thus the strong possibility that the secretion of P somehow causes an autoimmune stripping off of the thick walls of some of the uterine arteries with a subsequent addition of a one cell layer from cells from the extra villus trophoblast on day 6 when there is invasion into the endometrium by the fetal-placental unit to allow stability of the vessels [1-3].

The hypothesis suggests that to facilitate the necessary cellular immune cells that are needed for the autoimmune stripping off the cell walls of certain targeted thick-walled vessels to occur shortly after ovulation the increased secretion of progesterone blocks the biogenic amine dopamine. One of the functions of dopamine is to decrease cellular permeability. Thus, the hypothesis considers that the increased cellular permeability that occurs from blocking dopamine by P allows potentially inflammatory irritants to traverse the mucosal barrier stimulating a cellular immune response consisting predominately of natural killer cells (70%), macrophages (20%), and cytotoxic t cells (10%) [1-4].

The hypothesis continues that women with various types of pelvic pain, including chronic pelvic pain, mittelschmerz, dysmenorrhea, and dyspareunia may have a problem with increased tissue permeability in their pelvic tissues that allows the infiltration of excessive irritants that causes a greater inflammatory reaction than necessary for normal procreation leading to pelvic pain of one type or another [5,6]. Excessive inflammation may lead to autoimmune rejection of the fetus because the body's normal mechanism of suppressing this increase in cellular immune activity by P leading to the production of immunosuppressive proteins by the interaction of P with mPRs may be insufficient to negate an excessive inflammatory response from harming the fetus [7,8].

Thus, some of these types of pelvic pain syndromes may occur only at mid-cycle or the luteal phase or at the time of menses because the secretion of P further enhances cellular permeability [9]. However, some of these pelvic pain conditions may occur throughout the entire cycle and are not exclusively exacerbated during the luteal phase. This would imply a pelvic tissue permeability defect present even without the extra defect with P secretion.

The cause of increased tissue permeability may be multifactional and could be related to a genetic defect, infection, or trauma to name a few. One possible genetic factor could be one that leads to relative inadequate dopamine secretion leading to susceptibility of various tissues to infiltration of unwanted irritants and thus produce various extra pelvic symptoms besides pelvic pain [9,10].

This hypothesis is supported by the fact that not only have some types of pelvic pain co-existed with extra-pelvic pathological entities, but the pelvic pain and these other conditions respond also to dopamine agonist therapy [3,10]. Case reports have been published showing association of dyspareunia with interstitial cystitis and migraine headaches, or dysmenorrhea, chronic pelvic pain, and mittelschmerz linked with Crohn's disease, or chronic pelvic pain and very severe diarrhea related to microscopic colitis, or vaginismus and facial premenstrual eczema [9-11]. In all of these cases not only did the pelvic pain dissipate greatly with the treatment with the dopamine agonist dextroamphetamine sulfate, but so did the extra pelvic symptoms [9-11].

One would get the impression by these aforementioned reported cases with association with other problems that the defect in permeability is predominately in the pelvis and abdomen with associated entities as Crohn's disease, microscopic colitis, and interstitial cystitis [5,9-11]. The present case reported here illustrates some of the other extra pelvic pathological entitles that can also be associated with pelvic pain. Furthermore, it shows that not only does treatment with dopamine agonists provide significant relief of dysmenorrhea, but marked amelioration of these other symptoms also.

Case Report

A 35-year-old woman sought help with her severe dysmenorrhea. She not only desired to ameliorate the pain because of the suffering, but thought that it could be indicative of endometriosis. She desired a treatment that could eradicate the pain, but at the same time improve her likelihood of achieving a pregnancy in 6-12 months when she would actually start trying to conceive.

From speaking with friends and relatives who received various treatment options from their gynecologists, she was familiar with some of the suggested medical options including oral contraceptives, with and without the presence of the estrogen component, gonadotropin releasing hormone (GNRH) agonists e.g., depot-leuprolide acetate, and GNRH antagonists e.g., elagolix [12-20]. Her gynecologist, however, suggested laparoscopy to determine if there was the presence of superficial endometriosis or endometriosis and if so, to treat it with laser [21,22]. Alternatively, her gynecologist suggested she could refer the patient to an endometriosis surgeon who can surgically excise each of the endometriotic implants [23-26].

Our advice was not to treat with any of the options she was familiar with, but to consider the dopamine agonist dextroamphetamine sulfate (DS). We familiarized her with the condition known as the increased cellular permeability syndrome causing infiltration of inflammatory agents into various tissues e.g., including, but not limited to, pelvic organs [3,5,10]. Because

dopamine diminishes cellular permeability, it is likely to be more effective in treating her pelvic pain than medical or surgical therapy. Furthermore, it is common for this increased cellular permeability syndrome to not only cause pelvic pain, but also other conditions related to increased cellular permeability. Thus, we thought in addition to ameliorating her dysmenorrhea, DS could also ameliorate some of her other symptoms e.g., severe frequent headaches, lightheadedness when standing suddenly, her irritable bowel syndrome manifesting both with constipation at times and diarrhea at other times, urinary urgency and frequency, and her inability to lose weight despite dieting [27].

We advised her that we were not sure what effect DS would have on her anxiety since DS also releases epinephrine and norepinephrine. Thus, in some instances anxiety is worsened by DS. However, if the anxiety is caused by infiltration of unwanted elements into that part of her brain that controls emotions as the etiologic factor, the DS could help the anxiety problems. Similarly, DS could make her palpitations worse related to the catecholamine increase or could reduce them if the etiologic factor was irritants infiltrating heart tissue.

She started at 15mg amphetamine salts tablets (9.4mg DS) upon arising and noon and increased over 3 months to 30mg amphetamine tablets twice daily. She stated that she had marked improvement in the dysmenorrhea, headaches, urinary urgency and frequency, and light headedness. She is 64 inches tall and initially weighed 174.5 pounds. After 3 months of taking DS, she lost 15 pounds without any change in diet.

Her anxiety markedly improved with DS. There was no change in the frequency or severity of the palpitations which were only occasional anyhow. Interestingly, she had long intervals between menses and her intervals had shortened. Since she was not trying to conceive as yet we never ascertained whether her previous long intervals between menses occurred with ovulation or anovulation or whether she is now ovulating or not.

Discussion

From our clinical experience we find that dopamine agonists provide better relief of pelvic pain than standard treatment options including surgery [4]. From our own experience we do find that surgical treatment of endometriosis can not only relieve pelvic pain at least transiently, and in a minority of cases for long periods of time, but can improve fecundity [28]. However, our clinical experience suggests that not only does dopaminergic agonist therapy provide superior relief of pelvic pain disorders compared to surgical therapy, but it has many advantages over surgery for correcting infertility or help prevent a fertility problem subsequently in women seeking help with their pelvic pain, but who wants to conceive at a later time as in the case reported here [29]. Pelvic pain and endometriosis are known to be associated with diminished oocyte reserve [30]. There is evidence that the use of dopaminergic drugs can either slow down the rate of egg depletion or even increase the conversion of primordial follicles to primary follicles and thus even increase serum AMH levels [31].

The gynecologist frequently acts as the primary care physician for women. Sometimes a patient may seek a consultation with her generalist in obstetrics and gynecology (OB-GYN) seeking help for infertility. Related to the fact that so many reproductive endocrine infertility (REI) specialists are geared toward recommending in vitro fertilization embryo transfer to solve infertility issues, related to the expense of the procedure, it behooves the generalist in OB-GYN to help solve the infertility problem without the aid of assisted reproductive techniques first [32].

Sometimes infertility may be related to immune rejection of the fetus related to increased permeability of pelvic tissues without pelvic pain, but instead may be associated with other manifestations of the increased cellular permeability syndrome e.g., Crohn's disease, ulcerative colitis, and severe chronic constipation [5, 31-37].

IVF-ET does not overcome the increased cellular permeability of pelvic tissues, leading to autoimmune rejection of the fetal semi-allograft. Thus, dopamine agonist therapy may be needed for successful outcome of women needing IVF-ET for conception related to tubal or male factor issues [38]. Unfortunately, despite many case reports and case studies of the role of excessive tissue permeability leading to irritating elements crossing the mucosal barrier causing inflammation and organ dysfunction in a plethora of medical conditions, this beneficial treatment with dopamine agonists does not seem to be known by the majority of physicians in internal medicine, OB-GYN, or other subspecialties [3]. This emphasizes the importance of the specialist in OB-GYN to be familiar with this condition since the generalist in OB-GYN may be required to treat these extra pelvic clinical entities to prevent not only less effective therapy by other physicians, but much more expensive immunosuppressive therapies that may also subject the women to risk of cancer and serious infections.

The case of the woman who had 12 years of 8-12 painful bowel movements per day that had not responded to corticosteroids or immunosuppressives targeting tumor necrosis alpha (TNF alpha) provides such an example [35]. Her last immunosuppressive drug for her stage IV Crohn's disease was adalimumab [35]. Her inflammation was present in the entire colon, but there was one segment that was most inflamed. The suggestion by the gastrointestinal specialists at a world-renowned university hospital was to perform a partial colectomy removing the severely inflamed bowel segment and construct a diverting ileostomy, double the dosage of adalimumab, rest her bowel for 8-12 months, then reconnect her. If the symptoms returned, they would then recommend a total colectomy.

She heard of our treatment with dopamine agonists, and thus she was treated with DS. Within a short period of time, she was reduced to one painless bowel movement per day [35]. She

did well for several years solely treated with the amphetamine when she decided to try to become pregnant at the age of 42 (this part of her case has not been previously published). Besides dextroamphetamine sulfate, she was treated with supplemental vaginal P suppositories in the luteal phase and ethinyl estradiol to lengthen her shortened follicular phase related to mild diminished oocyte reserve [39-43].

She conceived with natural intercourse after just a few months of the above therapy. She continued the dextroamphetamine throughout the first trimester when she was discharged to her previous OB-GYN at the same university medical center as her gastroenterologists. The OB-GYN referred her to maternal fetal medicine who advised her that autoimmune conditions, e.g., Crohn's disease, will usually go into remission during pregnancy and thus advised her to stop the DS. Her severe symptoms of Crohn's subsequently returned. She was advised to re-consult her GI specialist, who ignored her tremendous beneficial response to amphetamines and suggested the partial bowel excision with diverting ileostomy during the second trimester. She delivered a healthy baby. After one year of high dosage adalimumab, they reconnected her bowel. Within 1 month her multiple bowel movements with severe dyschezia returned. The GI specialist recommended a total colectomy. However, she returned to our practice, and we re-started the amphetamine, and her symptoms were again completely dissipated. Though she is no longer interested in having another baby, we continue to treat her Crohn's disease while seeing her for otherwise routine gynecologic care. This case underscores the possible role of the gynecologist who is familiar with dopaminergic therapy to continue with such care for these extra pelvic conditions in lieu of referring her to other specialists who would not be as familiar as the OB-GYN with the increased cellular permeability syndrome, and the beneficial treatment with dopamine agonists.

There is evidence that the increased cellular permeability syndrome is the most common cause of diminished oocyte reserve (DOR) [21]. This is commonly seen in women with pelvic pain even before surgical treatment of endometriosis which can further deplete oocyte reserve [29]. However, it may also be found in women who have other manifestations of this disorder even in the absence of any type of pelvic pain. Treatment with dopamine agonists can correct infertility problems when other conditions are present, but pelvic pain is absent [33,34,36].

There also evidence that dopaminergic agonists can not only inhibit the rate of oocyte depletion in females with this condition manifesting solely with a non-gynecological condition but may actively increase oocyte reserve if used at a young reproductive age. An example of this was a recent publication of a 14-year-old with unexplained mid-epigastric pain only induced by eating who had borderline DOR as evidenced by a serum anti-mullerian hormone (AMH) level of 1.03ng/ml (DOR considered with AMH of less than 1ng/ml.) Not only did her mid-epigastric pain completely resolve with DS therapy, but her serum AMH measured every 3 months steadily increased so that at the time of reporting her case her serum AMH had increased to 2.55 ng/ml [31].

The inheritance of this condition seems to be polygenic [45]. Interestingly, the mother of the aforementioned 14-year-old female with mid-epigastric pain went into complete menopause in her mid thirties. She never had any pelvic pain and/or still does not have any clinical manifestations of the increased cellular permeability syndrome. Thus, another important reason why the generalist in OB-GYN or REI's should continue to treat women with non-gynecological conditions and/or gynecologic conditions that respond to dopaminergic drugs is to prevent oocyte depletion in their children by intervening with dopamine agonists by careful monitoring of AMH in their children for evidence of relative deficiency of egg reserve according to age group. If relative DOR is found, one could not only recommend dopaminergic agonists to retard egg depletion, but consider oocyte cryopreservation.

Other dopamine agonists besides dextroamphetamine that can be used to treat both pelvic and non-pelvic manifestations of the increased cellular permeability syndrome include cabergoline and carbidopa levodopa [46-49].

Embarrassingly, many of the references provided were from our own group. This is mostly related to despite our publications dating back to 1984, for some reason, until very recently, this concept has not convinced the majority of physicians to prescribe this medication for both gynecologic disorders and extra gynecologic disorders [50]. It is the only therapy provided for pelvic pain and endometriosis that allows the patient to continue to try to conceive while taking the medication [29]. Obviously progestins, gonadotropin releasing hormone agonists and antagonists prevent pregnancy. Thus, for women who already may have DOR, this delay in attempting to conceive may allow further egg depletion. Surgical removal of endometriosis implants in the short term may improve infertility but may be at the expense of causing further depletion of egg reserve [29].

It is more credible if results can be corroborated in another center. Indeed, one of our publications reporting the benefit of using DS for pelvic pain was used by patients solely from the practice of one of the co-authors, Dr. Carpentier [4]. In preparation to write the case report of combining dextroamphetamine with cabergoline to prevent tardive dyskinesia while treating stomatodynia (burning mouth syndrome), we did a literature search of stomatodynia and vulvodynia. These studies were referred to in our review of the this condition [51]. One of these references should be noted. A study by Ford et al in 1996 found complete resolution of vulvodynia in all of the female patients who had this problem of vulvodynia and Parkinson's disease who were treated with carbidopa levodopa for the Parkinson's Disease [52].

Our group has published many case reports of treating headaches in women as well as men with dopamine agonists especially, but

not limited to, DS [53-62]. Similarly, we have published our own positive experience using DS to treat interstitial cystitis [63, 64]. The patient reported here with urinary urgency and frequency but without dysuria may have had a mild form of interstitial cystitis. We have previously reported a woman who had pelvic pain, headaches, interstitial cystitis similar to our patient but in her case the pelvic pain manifested as dyspareunia, her headaches were ocular but only premenstrual, and her interstitial cystitis included severe dysuria [9]. DS has also completely abrogated severe urinary incontinence from a neurogenic bladder [65].

A combination of headaches and vasomotor symptoms without pelvic pain has been reported to be markedly ameliorated by DS [55]. Dopamine agonists can improve vasomotor symptoms in both menopausal women and euestrogenic women [66,67]. The hypothetical mechanism is to tighten the mucosal barrier preventing infiltration of irritants into the brain which may disrupt the temperature regulation center.

The improvement of the diarrhea and constipation of the patient reported here with DS is not surprising since DS has been bound to markedly improve severe treatment refractory disorders of diarrhea and constipation [5,33-37,68].

There is evidence that the increase in hydrostatic pressure upon standing that occurs in the human species would cause fluid to traverse from the intravascular space to the extravascular space were it not for the change in posture evoking a release of dopamine from sympathetic nerve fibers causing decreased capillary permeability. Relative inadequate dopamine release or a delay may lead to accumulation of fluid in the interstitial tissues leading to a brawny non-pitting edema and weight gain [69,70]. There is evidence that dopaminergic drugs, e.g., DS can cause weight reduction in diet-refractory women [69,70]. We attribute her 15-pound weight loss in just 3 months to be related to inhibiting fluid retention.

The orthostatic light-headedness that was one of the reported patient's extra pelvic symptoms could have been related to a mild form of postural orthostatic tachycardia syndrome (POTS). When the vascular permeability defect is mild, the symptoms are edema and weight gain, and it is referred to as idiopathic orthostatic edema [71]. If the permeability defect is more severe, leading to a temporary decrease in circulatory blood volume, with subsequent decreased ejection fraction of the heart, there may be light headedness or syncope. The light headedness that markedly improved in this patient with dopamine agonist therapy has been found to be very effective in very severe long-term cases of POTS [72].

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