ISSN: 2755-6204

Case Report

Journal of Sexual Health and Reproductive Medicine

Besides Abrogating an Unusual Case of Eating Induced Mid-Epigastric Pain, Treatment with Dextroamphetamine May Help to Increase Oocyte Reserve in A Young Teenage Girl Possibly Heading for Premature Menopause

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Received: August 28, 2025; **Accepted:** September 04, 2025; **Published:** September 12, 2025

ABSTRACT

The increased cellular permeability syndrome where inflammatory conditions related to unwanted irritants infusing into various tissues related to local permeability issues is etiologic in many different types of abdominal pain. These abdominal conditions and many other pain syndromes have been completely abrogated by treatment with the dopamine agonist dextroamphetamine sulfate. The most frequent cause of diminished oocyte reserve (DOR) and premature ovarian failure (POF) is increased permeability of the ovaries leading to inflammatory damage and loss of eggs. A 14-year-old teenager whose mother had premature ovarian failure, brought her 14-year-old daughter for evaluation of severe pain with eating. Pediatric gastroenterologists were stumped as to the cause of abdominal pain. As part of her evaluation, we obtained a serum anti-mullerian hormone (AMH) level which was found to be low normal even for an adult. She was treated with dextroamphetamine which completely eliminated her pain from eating for 2 years now. We were hoping that this dopamine agonist could slow down the rate of egg loss to give her time to advance to a late teenager rather than consider egg freezing in someone so young. We were very surprised that after 2 years not only did her serum AMH not drop any further but actually increased to a level of 2.5 ng/mL which is at a much more comfortable level of egg reserve. This case suggests that reducing the cause of ovary inflammation by the use of dopamine agonist may not only retard egg depletion but even allow more oogenesis to occur.

Keywords: Dopamine Agonist, Diminished Ovarian Reserve, Prandial Abdominal Pain, Increased Cellular Permeability Syndrome

Introduction

There is evidence that an essential part of a successful pregnancy is to develop spiral arteries to allow nutrient exchange between mother and fetus. One model proposes that the majority of these spiral arteries that start to evolve during the luteal phase, since neovascularization is a slow process, the model proposes that the main mechanism is to strip off the thick walls of the uterine arteries found during the proliferative phase by autoimmune mechanisms involving natural killer cells, macrophages, and cytotoxic T cells [1-3]. The model proposes that a key factor in stimulating the autoimmune response is that progesterone (P) blocks dopamine. One of the functions of dopamine is to diminish cellular permeability which may allow unwanted irritants traversing the normal mucosal barrier leading to an inflammatory response [1-3]. Of course, it would then be necessary to suppress these inflammatory cells from attacking the fetal semi-allograft. According to this model the suppression of these immune cells from attacking the fetus is by the concomitant interaction of P activating membrane progesterone receptors (mPRs) to make certain immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) [1-4].

As an extension of this implantation model consideration was given to the concept that autoimmune conditions and other chronic disorders may have as their basis increased cellular permeability leading to infiltration of irritants into various tissues causing inflammation or organ dysfunction. Evidence to support this concept is supported by the marked improvement of various treatment refractory disorders involving almost every organ system of the body following treatment with dopamine agonist drugs, especially, but not limited to dextroamphetamine sulfate [3,5].

Citation: Jerome H Check, Naomi Ganpo-Nkwenkwa, Priya Srivastava. Besides Abrogating an Unusual Case of Eating Induced Mid-Epigastric Pain, Treatment with Dextroamphetamine May Help to Increase Oocyte Reserve in A Young Teenage Girl Possibly Heading for Premature Menopause. J Sex Health Reprod Med. 2025. 1(3): 1-5. DOI: doi.org/10.61440/JSHRM.2025.v1.24

There have been several case reports demonstrating quick effective relief of long-term abdominal pain and associated bowel dysfunction (e.g., diarrhea and constipation) including unexplained abdominal pain of 20-year duration, inflammatory bowel disease, gastroparesis, pseudo intestinal obstruction, chronic pancreatitis, and pathological after constipation it should read constipation following treatment with dopamine agonists [6-16].

The case reported here discusses an interesting case of unexplained food induced severe abdominal pain that also responded very well to treatment with dextroamphetamine sulfate. Even more importantly, this case may show that treatment with dextroamphetamine may not only help to delay further egg depletion in a female with diminished oocyte reserve (DOR) but may actually help to possibly restore egg supply.

Case Report

A 38-year-old woman consulted our practice regarding her diagnosis of premature ovarian failure and the possibility of future children though she was not interested in conceiving at that time. Her serum FSH was 75.8 mIU/mL. She states that she had oligomenorrhea since age 34, but she did conceive naturally and had a delivery of a full-term baby girl.

She was advised that there was a reasonable possibility that we could restore sensitivity of her few remaining follicles by lowering serum FSH and thus up-regulating down-regulated FSH receptors and freeze the embryos if she was not interested in conceiving at this time [17-19]. However, because of marital issues she did not want to proceed in that direction. Her daughter was one year old at that time. Though she eventually divorced her husband and never remarried, and she was not interested in another baby, she continued in our practice for routine gynecological care and to manage her estrogen/progesterone replacement and her hypothyroidism. She did not complain of pelvic pain or any other medical conditions. Her mother went into menopause at the normal age.

She brought her daughter in for evaluation of severe periumbilical pain that only occurred while eating. This condition was present for 9 months at the time of the initial presentation. It started out intermittently but had progressed to occurring with each meal. She stated that it had reached a point of intensity where she could not finish a meal. The pain was sometimes associated with the feeling of the need to defecate but she did not need to move her bowels so she just left the table and would lay down. The pain persisted for 15 minutes after she stopped eating.

She did have a history of acute appendicitis 2 years before and had an appendectomy. Neither her pediatrician nor her pediatric gastroenterologist thought the present symptoms were related to the previous appendectomy.

Though she had oligomenorrhea, she denied dysmenorrhea or any other type of pelvic pain. Despite early menopause, her mother did not have pelvic pain either. However, we find that the most common etiology for premature menopause is autoimmune damage to the ovaries related to infusion of unwanted infusion of irritants into the ovarian tissue eliciting a cellular immune response. The infusion of unwanted elements into ovarian tissue is most likely from increased cellular permeability. The mother did not ever have ovarian or abdominal surgery and no chemotherapy or radiotherapy that could have damaged the ovaries. Even though this autoimmune damage related to increased infusion of unwanted irritants is usually associated with other manifestations of the increased cellular permeability syndrome, especially pelvic pain, in the mother's case there were no symptoms [3,20,21].

The mother and daughter were explained about the increased cellular permeability syndrome which can manifest with different symptoms in the same family probably related to a predisposition to having relative dopamine deficiency, but the phenotypic expression could be different in family members according to the presence of other genetic factors in genes that may make another area of the body prone to inflammation related to paternal inheritance to sometimes different phenotypic expression may be related to exposure to certain viruses or bacteria or trauma. They were given an example of 4 siblings that had in common recurrent aphthous stomatitis (RAS) with one female having very severe ulcers since age 4 for 20 years which completely dissipated following treatment with the sympathomimetic amine dextroamphetamine sulfate for its dopamine agonist actions to decrease cellular permeability. It also helped her edema and chronic fatigue [22-24]. Her teenage brother also had RAS but very extreme heat sensitivity [22,25,26]. Another sister had only mild RAS but had moderately severe dysmenorrhea [27-32]. Not only did the RAS of the aforementioned 2 siblings disappear but so did their other symptoms [22,25-32]. But the main reason for discussing this family was the 4th brother, who not only had RAS, but had a condition similar to the 14-year-old girl in that he could not finish a meal without pain. However, in his case, he had a severe urge to defecate, i.e., gastrocolic reflux [33]. Needless to say, all 4 siblings responded very well to treatment with dextroamphetamine sulfate [22,33,34].

We also discussed another case to support our opinion to forgo gastroscopy which was the recommended next procedure to perform in an attempt to find a cause of her symptoms which could hopefully lead to a successful treatment and just try treatment with dextroamphetamine sulfate. The case we prescribed was a generally very tough longshoreman who suddenly developed a problem of very severe mid epigastric pain that only occurred with eating that was so intense for 20 minutes that he would roll on the floor in pain and sometimes begin crying. He also had 25 episodes of emesis per day. He was evaluated by many gastrologists at several world-renowned medical centers. They were stumped with his diagnosis until he was evaluated at the Mayo Clinic in Rochester, Minnesota. Their diagnosis was a rare condition of mesenteric sclerosis. They stated that his pain with eating was related to marked narrowing of his mesenteric arteries and hypoxia to his bowel was exacerbated by eating which would divert the blood flow to his gastric arteries. He was advised that there was no treatment and that he probably would die in the near future related to bowel perforation. The mother and daughter were advised [33] after 1 month of 15mg immediate release tablets of amphetamine salts upon arising and at noon providing 18.8mg of the active ingredient dextroamphetamine sulfate he no longer had pain with eating, and he was able to eat

all types of food, and his vomiting completely stopped. He has been fine now for over 10 years [34].

Her mother, a research scientist, was in favor of starting therapy with amphetamine salts. However, her father was not. As a compromise, we started her on less than our usual starting dosage of 15mg immediate release tablet AM and noon and only used 10mg per day in the AM. Her symptoms only mildly improved at 10mg, so an extra 5mg was added at 3pm to be closer to the dinner meal. This was eventually increased to 10mg AM and 3PM which completely corrected her periumbilical pain with eating. She was also able to have snacks later in the evening without pain. Interestingly if the dinner, which was usually between 6-7PM, was delayed by 2 hours, though she would not experience pain she but would have early satiety. Our only investigative studies were to obtain an 8AM serum cortisol to exclude adrenal insufficiency as a cause of abdominal pain and thyroid studies. Both were normal.

Related to her oligomenorrhea, with menses starting at age 12, but with her mother's history of premature ovarian failure (POF), we evaluated the daughter's serum FSH, which was 10mIU/mL and thus relatively high for a 14-year-old girl, and her serum estradiol was 63.1 pg/nl. Somewhat diminished ovarian reserve was confirmed by a relatively low serum anti mullerian hormone (AMH) level for her age of 1.34 ng/ml. Chromosome analysis revealed a normal 46xx female. She was given the option of egg freezing or careful observation to see if the theoretical prevention of further ovarian damage by dextroamphetamine could push her to an age when egg retrieval would not be so emotionally damaging or even possibly improve ovarian function. Three months later her serum AMH was a little higher at 1.60 ng/ml and 2 months later increased to 1.77 ng/ml. At present, 1.5 years while being treated with dextroamphetamine sulfate her serum AMH is at a much more comfortable level of 2.50 ng/ml.

Discussion

Thus, this case besides demonstrating another unusual manifestation of the increased cellular permeability syndrome, i.e., severe abdominal pain without diarrhea induced by eating responding very well to dextroamphetamine, also demonstrates that not only may this therapy slow down the rate of egg depletion, it may actually allow increased oogenesis.

In the absence of documenting an X chromosome abnormality, or known history of ovarian surgery, chemotherapy, or radiotherapy most cases of DOR or POF are idiopathic [35]. Recent conclusions from Shekari et al suggests that in most women POF is not caused by autosomal variants despite the suggestion from studies published previously [36]. Shekari et al thus conclude that most cases of DOR or POF are polygenic or oligogenic in nature [36]. Many genes have been involved in POF etiology participating in the biological processes in the ovary. MCM8 gene pathogenic variants are involved in meiosis, DNA damage repair, homologous recombination and chromosomal instability [36]. There are also several transcription factors including FOXL2 and NOBOX which variants forms play a role in dysfunction in follicular development, granulosa cell differentiation and proliferation leading to POF [36]. Therefore, the identification of those different pathogenic variants endorses polygenic etiology of POF [36].

There is good evidence that the increased cellular permeability syndrome has a polygenic etiology [36]. Our observation of the increased cellular permeability syndrome is that there is an inheritance for either specific tissue to have flaws in the mucosal barrier that makes the tissue more susceptible to infiltration of irritants which can cause pain, but also organ damage. Sometimes the tissue is able to preclude infiltration of irritants but is more susceptible than areas of the body without the defect or injury to infection by bacteria, fungi, or viruses now leaving that tissue permanently damaged. The restoration of partial or full mucosal barrier protection can be restored by pharmacologic treatment with dopamine agonists which functions to diminish cellular permeability.

Related to inheritance sometimes one type of tissue may be more likely to be susceptible to inadequate mucosal barrier issues leading to similar symptoms in parents and child. For example, it is not uncommon for mother and child to have severe dysmenorrhea related to increased cellular permeability which may lead to escape of endometrial tissue to extra uterine locations resulting in the presence of endometriotic lesions [37]. Inflammation can cause ovarian damage and can lead to DOR or POF even in the absence of further damage by surgery [19,20,38]. A perfect example of the polygenic nature of the increased cellular permeability syndromes was to report with 4 siblings who had various degrees of recurrent aphtous stomatitis (RAS) from very severe to mild but who each had different other pathological conditions e.g. chronic fatigue, edema, gastrocolic reflux, or dysmenorrhea [39]. One could argue that these other entities have other etiologies than increased cellular permeability syndrome. However, what suggests that these other entities are indeed linked to a general tendency for increased cellular permeability was the fact that all of these various co-morbidities resolved with treatment with the dopamine agonist dextroamphetamine besides complete resolution of the RAS [39].

Since the mother of the case reported here also had POF without any pelvic pain or other clinical manifestations of the increased cellular permeability syndrome, one may have argued that her POF was not caused by inflammatory damage of the ovaries but rather a different etiology. However, the fact that her daughter, despite the absence of pelvic pain, had borderline egg reserve for an adult as evidenced by normal serum FSH and a low normal AMH, and yet had severe pain with eating which was resolved by treatment with dextroamphetamine sulfate, suggests that one can have increased cellular permeability of some tissues but without clinical manifestations as seen in the mother. It also shows that related to another gene possibly inherited from the father or different penetration from a gene from the mother, or the exposure to a nongenetic environmental factor, the daughter, but not the mother, manifested with a new clinical presentation of the increased cellular permeability syndrome (mid-epigastric pain with eating) that showed complete resolution following treatment with a dopamine agonist.

The hope for patients with DOR is that dopaminergic drug therapy could retard the rate of egg depletion. However, this would be hard to prove in just one case because how can one be sure how fast egg depletion was to occur. We have seen successful pregnancies x3 with their own eggs over an 8-year

time span in two women with DOR [39,40]. Interestingly, one of these women was taking dextroamphetamine during this time but the other woman was not being treated with a dopamine agonist [40,41].

The major importance of this case report is not only evidence that dopamine agonist treatment can not only retard the rate of egg depletion in women prone to acerated rates of egg atresia, but that this therapy may be able to restore egg depletion possibly if detected early enough. We will be watching her serum AMH levels every 6 months and hope to find a steady increase or at least a stable holding pattern. Obviously, if the serum AMH starts dropping again, we may need to consider oocyte freezing.

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