

# A Case Illustrating Many Advantages of Treating Endometriosis and Pelvic Pain with Dopamine Agonists Rather than Surgery or Other Medical Options

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## Abstract

**Background:** There is a growing number of medical management and surgical procedures for chronic pelvic pain syndrome frequently associated with endometriosis. However, generally, when there are multiple treatments for a given pathological disorder, usually not any of them are highly effective for this problem. Over the years there has been an increase in case reports demonstrating marked relief of various pelvic disorders following treatment with dopaminergic drugs especially dextroamphetamine sulfate (DS). The theoretical reason for this treatment was based on experimental evidence that dopamine functions to diminish cellular permeability. This increased cellular permeability of pelvic tissues, whether genetic or acquired from infection or trauma, allows the infusion of excessive irritants leading to inflammation and pain.

**Case report:** A 28-year-old woman sought an opinion on how to alleviate pre-menstrual pain and very severe dysmenorrhea. The pain was treatment resistant to non-steroidal anti-inflammatory drugs NSAIDS and oral contraceptive OCP's, only manageable with parenteral narcotics. DS treatment allowed considerable pain relief for 5 years, until one cycle following one cycle with menorrhagia she had a mild episode of dysmenorrhea which led her to have a laparoscopy before her medical insurance lapsed. Following the removal of endometrial implants removal she stopped DS. However, on her 4th cycle post-surgery, she developed severe dysmenorrhea causing the need for parenteral narcotics. After getting a diagnosis of possible adenomyosis, she underwent hysterectomy. However, post-surgery pathology results were negative for adenomyosis. She subsequently developed unbearable symptoms associated with interstitial cystitis. She was once again prescribed DS which completely abrogated her daily bladder pain and urgency and frequency.

**Conclusion:** Disorders of the sympathomimetic nervous system may be a cause of chronic pelvic pain and are relieved by treatment with dopamine agonists. This case supports the concept that pelvic pain is not so much from the presence of inflammatory endometriotic implants but increased pelvic tissue inflammation and pain related to increased cellular permeability. Another advantage of dopamine agonists over surgical therapy for endometriosis is that the former can also effectively treat other co-morbidities associated with endometriosis, e.g., interstitial cystitis.

## Introduction

Chronic pelvic pain (CPP) is a common and burdensome condition which is present in 15% of the US population disproportionately affecting women [1]. Annually, it accounts for 10% of all gynecology office visits, 40% of laparoscopies, and 12% of hysterectomies, [1,2]. CPP is defined as pain perceived to arise from the pelvic structures, lasting more than 6 months [1-2]. CPP is a complex condition, and even in

modern times the underlying pathophysiology is still not understood. There are several other negative factors which intersect with the condition, including defective cognitive, behavioural, and emotional disorders [1-3]. The most frequently identified condition associated with CPP is endometriosis. It has been estimated that it is present in 10% of all reproductive-age women and 70% of those with CPP [4-8].

Endometriosis is a systemic chronic and inflammatory gynecologic



condition defined by the presence of endometrial-like tissues outside of the uterus, commonly on the ovaries and pelvic peritoneum [4-8]. Regarding the development of endometriotic lesions, the most common proposed mechanism is retrograde menstruation [6-9]. During the menstrual cycle there is an outflow of the endometrial lining through the patent fallopian tubes into the pelvic space resulting in the seeding of endometrial ectopic tissue assisted by circulation of lymphatic or hematogenous circulation [6-9]. It is implied that for women who develop endometriotic lesions there must be some immune deficiency that prevents the probable normal ability of the body to remove these implants and prevent mitosis of these aberrant endometrial cells.

The clinical presentation of endometriosis is heterogenous and varies overtime. It can be diagnosed incidentally during laparoscopic procedures performed for other indications in asymptomatic patients. It is important to recognize the three subtypes of pelvic endometriosis as they may affect the presentation. Superficial peritoneal endometriosis is the most common subtype defined by lesions of various sizes and colors localized at the surface of peritoneum, which can only be diagnosed laparoscopically. Another subtype is endometriomas which are ovarian cysts which contain dark blood-stained fluid, known as "chocolate cysts" [10,11]. They can be diagnosed with a transvaginal ultrasound. Lastly, there is deep endometriosis, which are lesions that extend beyond the peritoneum and can invade pelvic organs [10-12]. They have the capacity to cause end-organ damage, so prompt diagnosis through transvaginal ultrasound is very important for further clinical management [10-12].

The most common type of pelvic pain is dysmenorrhea [7,8,10]. Other symptoms include non-cyclic pain (which may or may not intensity during the menses), painful sex (dyspareunia), mittelschmerz (painful ovulation), and infertility [4-10]. Deep endometriosis that invades adjacent structures can present with pain on defecation (dyschezia) and/or urination (dysuria), bloody stools (hematochezia) or hematuria [10-12].

Thus, overall, the severity ranges from mild to debilitating pain. It can be episodic (mostly associated with menstrual cycle) or constant. The severity of the anatomical endometrial lesions does not necessarily correlate with the severity of the pain. Furthermore, endometriosis commonly presents with co-existing conditions such as vulvodynia, irritable bowel syndrome (IBS), and painful bladder syndrome, also known as interstitial cystitis (present in nearly 50% of patients) [4-10].

The gold standard for definitive diagnosis of endometriosis is laparoscopic visualization confirmed with histopathology which would describe "endometrial glands and stroma with inflammation and fibrosis" [10-13]. Ultrasonography and Magnetic Resonance Imaging (MRI) can be used to diagnose endometriosis preoperatively; however, the absence of findings does not exclude endometriosis, especially the superficial type with peritoneal lesions [5-10]. The lesions physically have various sizes including nodules or cysts and different colors including classic "gunshot powder", with blue, black, red, transparent and brown colors [13-15].

Most women report onset of endometriosis symptoms during adolescence. However, there are several barriers to early diagnosis including wait time for surgical exploration and confounding symptoms such as cyclic and acyclic pain [6]. There are several differential diagnoses for dysmenorrhea which makes it difficult to isolate endometriosis as they can co-exist with the condition. Severe pelvic pain of various types may be found with adenomyosis.

## Medical management

Many medical therapies for pain are often tried empirically based on clinical symptoms without a tissue diagnosis of endometriosis [13]. The ectopic endometrial tissue has been found to have increased production of estradiol, intrinsic aromatase activity, production of

inflammatory markers, and resistance to progesterone [16-18]. Therefore, medical management has a goal to suppress those processes to provide relief for patients.

According to international guidelines and the American Association of Obstetricians and Gynecologists, first line medical treatment for endometriosis-related pain is non-steroidal anti-inflammatory drugs (NSAIDs) given their low side-effect profile and easy availability over the counter (OTC) [8,11,16-18]. Another first-line treatment which can be offered in the primary care setting in adjunct to NSAIDs or NSAIDs refractory patients is hormonal therapy including combined estrogen-progestin or progestin only medications. They are low-cost medications which work by targeting sex-steroid dependent pathophysiology.

They function by suppressing ovarian activity inducing anovulation and inhibiting estrogen activity, which can lead to regression of endometrial lesions [16-18]. Some adverse effects of these drugs are heavy vaginal bleeding, vaginal dryness, reduced libido, breast discomfort, sleepiness, and depression [16-18]. Guidelines recommend continuous use of progestin contraceptives by omitting the hormone free interval to induce amenorrhea [16-18]. Progestin-only therapy has been shown to effectively act locally and reduce the risk of thromboembolism compared to combined oral contraceptive pills (OCP) [18]. If the patient does not respond to NSAIDs and/or OCP's within 3 to 6 months, a second-line treatment should be considered.

Second-line hormonal treatment includes gonadotropin-releasing hormone (GnRH) agonists and antagonists, e.g., leuprolide and elagolix. The GnRH antagonist (elagolix) is an oral pill. Once discontinued, there is a rapid return to regular menstruation cycle [18,19]. GnRH agonists and antagonists are expensive and have menopausal symptoms as side effects including decreased bone mineral density and vasomotor symptoms [17, 18]. To mitigate the menopausal side effects, it is recommended to co-administer hormonal therapy with combined estrogen-progestin hormonal therapy or norethindrone acetate [8,11,16-18].

A new class of drug called aromatase inhibitors (AI) which are considered third line treatment are indicated for patient's refractory to all medications stated above. However, they are currently not FDA approved for the treatment of endometriosis. They differ from other options which work by inhibiting estrogen function and estrogen production by inhibiting gonadotropins but instead focus on blocking estrogen produced locally in endometriotic lesions. AI works by blocking aromatase P450 enzyme, the final enzyme in the estrogen biosynthesis pathway, resulting in reducing the size of endometriotic lesions and pelvic pain [17-19].

## Surgical Management

If the symptoms of pelvic pain persist, despite medical therapy, or if adverse effects outweigh the beneficial effects of drugs, or drug therapies are contraindicated (patients want to conceive) then surgical treatment is frequently recommended [8,11]. In patients with deep endometriotic lesions which have led to ureteric or bowel obstruction, or endometriomas of any size that have features concerning for malignancy (> 4-5cm) or ovarian torsion, surgery may also be the only management option [8, 10,16-18]. Furthermore, the nonsurgical options discussed above can be used to supplement surgical treatment for better long-term results [20, 21].

For superficial endometriosis, recent randomized trials suggest no significant differences between excision and ablation of endometriosis in reducing long-term dysmenorrhea, dyschezia and chronic pelvic pain when evaluated at 12 months of follow up [22,23]. Furthermore, there is no clear consensus on the most effective surgical treatment for advanced endometriosis, which may involve peritonectomy, bowel shaving, discoid or segmental bowel resection, and more [22].

Specifically for the treatment of endometriomas, the European Reproductive Society of Reproduction and Embryology (ESHRE) guide-



lines recommend considering both cystectomy and CO<sub>2</sub> laser vaporization, instead of drainage and coagulation as both techniques have similar reduced recurrence rates and endometriosis associated pain [11]. However, according to a meta-analysis, ovarian cystectomy may harm fertility as shown by a 38% reduction in postoperative anti-müllerian hormone levels (marker for ovarian reserve) [18,23]. Recent systemic review and meta-analysis have shown that the treatment of endometriomas with laser vaporization using CO<sub>2</sub> has shown more benefits in ovarian reserve level after the intervention [24].

Hysterectomy for endometriosis is an option reserved for women who no longer wish to conceive, who have not responded to more conservative management, or who have a coexisting diagnosis of adenomyosis [5,8,11]. It is accompanied by the removal of all visible endometriosis lesions; however, it still does not guarantee a “cure” for endometriosis. Additionally, it is associated with long term comorbidities including cardiovascular risk and menopausal symptoms [5].

Alternate Concept for Pathophysiology of CPP Leading to Unconventional but Highly Effective Medical therapy. There is evidence that a successful pregnancy requires the development of spiral arteries during the luteal phase and throughout the pregnancy term. These spiral arteries have a cell wall that is only 1 cell thick derived from extra villous trophoblast cells [25]. During the proliferative phase, most uterine arteries have thick cell walls. The development of thin-walled spiral arteries could be from neovascularization. However, the new development of organs or tissue or blood vessels is generally a genomic process, which is a slow process. The sudden appearance of these vessels in the luteal phase favors their development from a non-genomic process. This suggests that these spiral arteries may be created from remodeling the already existing thick-walled arteries which would likely occur related to an autoimmune process [25].

This embryo implantation model suggests that the autoimmune stripping of the thin-walled uterine arteries found in the proliferative phase is facilitated by the production of progesterone (P) in the secretory phase which blocks the biogenic amine dopamine [25]. According to the hypothetical model, since dopamine functions to diminish cellular permeability by interfering with the dopamine effect, irritating agents cross the mucosal barrier and thus stimulate a cellular immune response.

There is evidence that these inflammatory cells which theoretically help in the creation of thin-walled spiral arteries also invade the fetal-placental microenvironment [25]. The composition of these inflammatory cells are 70% natural killer (nK) cells, 20% macrophages and 10% cytotoxic T-cells [25].

In the balance of nature, one might think that if P helps to cause this inflammatory state, it will probably do something to counteract potential immune destruction of the fetal placental semi-allograft. Evidence suggests that at least one way that this is accomplished is by P activating fast-acting membrane P receptors (mPRs) to produce immunomodulatory proteins that suppress the killing activity of these cellular immune cells against the fetus. These proteins include the progesterone-induced blocking factor (PIBF) and the progesterone receptor membrane component-1 protein (PGRMC-1) [26,27]. Activating mPRs may also play a significant role in the way cancer cells escape immune surveillance. Thus, blocking the mPR by a PR antagonist seems to produce a significant halt to cancer progression leading to a marked improvement of length and quality of life in patients with advanced cancers [28-33].

According to the tenets of this concept of a mechanism for embryo implantation, the normal degree of inflammation needed to create spiral arteries is relatively painless. However, various types of pelvic pain may result from excessive inflammation in some of the pelvic tissues [34]. This increase in cellular permeability related to an excess of irritants infusing into pelvic tissues may be related to a polygenic generalized disorder of mucosal barrier defects coupled with a weak-

ening of a specific tissues related to additional monogenic or polygenic abnormalities of that tissue or acquired trauma or infection [35]. Alternatively, the polygenic initiating factor may be a generalized relatively insufficient dopamine response when a tissue is exposed to a noxious stimulus [35].

Evidence to support this theory has been provided by the demonstration of marked amelioration of pelvic pain of various types in small series or individual case reports demonstrating marked pain relief following treatment with dopamine agonists despite being refractory to standard treatments e.g., dysmenorrhea, dyspareunia, mittelschmerz, chronic pelvic pain, pelvic pain of bladder (interstitial cystitis) vulvodinia, vulvovaginitis, and dysorgasmia [36-45].

It is well known that pelvic pain with or without endometriosis may be associated with other medical conditions that may involve extra pelvic pain or functional abnormalities of extra pelvic structures. Dopamine agonists have been found to not only ameliorate the pelvic pain but also concomitant extra pelvic pain or organ dysfunction [46,47]. In fact, dopamine agonists have been used to treat pain from various conditions associated with pain when pelvic pain was not present [48-50]. Dopamine agonists have proven effective for pelvic pain when endometriosis is not present, but there is evidence of adenomyosis [51].

Most of the small case series and anecdotal case reports treating pelvic pain were treated by the dopamine agonist dextroamphetamine sulfate (DS) or other amphetamines e.g., lisdexamfetamine. DS is a sympathomimetic amine releasing dopamine from sympathetic nerve fibers. However, amphetamines also release other biogenic amines, e.g., epinephrine, and norepinephrine. Thus, the possibility exists that it is not the release of dopamine but other biogenic amines that are responsible for the improvement. However, supporting the hypothesis that it is dopamine providing the pivotal role is supported by both pelvic pain and extra pelvic pain relieved by pure dopamine agonists e.g. cabergoline or carbidopa-levodopa [52-56].

A case is presenting not only providing new insights into pelvic pain and the increased cellular permeability syndrome, but also a case emphasizing why dopamine agonist therapy should be much preferred over surgery for cases of severe dysmenorrhea failing to gain relief from standard medical therapy.

## Case Report

A 28-year-old woman sought an opinion on how to alleviate pre-menstrual pain and very severe dysmenorrhea. Her pelvic pain started with menarche but had intensified to the degree that for the last 2 years she needed to go to the emergency room to receive parenteral narcotics in at least 70% of her menstrual cycles. The other 30% of the time the pain was still severe but sufficiently tolerable with non-steroidal anti-inflammatory drugs and oral acetaminophen with codeine. The pain was not reduced at all by the use of oral contraceptives either taken cyclically or continuously because with breakthrough bleeding the pain was just as severe and required parenteral narcotics. Low dose norethindrone also caused breakthrough bleeding so frequently that she had pain most of the time, not just premenstrually and during menses.

We suggested dextroamphetamine sulfate in the form of amphetamine salts supplying 18.8mg of dextroamphetamine sulfate (DS) per 30mg amphetamine tablets. The dosage was gradually titrated up and at 60mg amphetamine salts with DS treatment, she had very little to no dysmenorrhea. The considerable pain relief lasted for 5 years until she was 3 weeks late for her menses. When her menses started, it was very heavy and she stated that the pain was the same intensity as the milder dysmenorrhea she used to have during the 30% of the time that she did not require parenteral narcotics. Nevertheless, she was leaving her job to pursue another type of independent work which meant that she would be losing her insurance. Though we advised her that sur-



gery would probably not be necessary because the dysmenorrhea was most likely related to the heavy bleeding, she sought a second opinion. The other consultant, a gynecological surgeon who specialized in the excision technique for endometriosis, convinced her that laparoscopic surgery was probably her best decision. He was not familiar with the use of dopaminergic drugs for treating dysmenorrhea.

He found 3 small endometriotic implants which were excised. He told her that she could stop the amphetamines because the surgery should be sufficient. Indeed, she had no dysmenorrhea for 3 menstrual cycles following the surgery. However, the pain was so severe with cycle 4 that she re-visited the emergency room again for parenteral narcotics. She advised the surgeon of the painful episode. He advised her that he was suspicious of adenomyosis because he was not convinced that all the pain that she experienced was caused by 3 small implants of superficial endometriosis. She agreed to a hysterectomy. Pathological examination did not find any evidence of adenomyosis. A few months later she developed dysuria, urgency, and frequency. Urine for culture and sensitivity did not grow out any bacterial pathogens in 3 samples evaluated at different time periods. The dysuria was becoming unbearable. She consulted a urologist who suggested to her that she had developed interstitial cystitis. She sought another opinion from our group, and we restarted amphetamine salts immediate release tablets 30mg upon arising and at noon. The dysuria, urgency, and frequency completely dissipated [43,44,46].

Her urinary symptoms were totally eradicated for the next 2.5 years with the exception of a couple of times when she failed to fill her prescription for amphetamines in time. She moved to another state, so we do not know if she is still being treated with DS or not. It should be noted that this single woman was nulliparous at the time of the hysterectomy. She said she agreed to the procedure because she did not think that she wanted to have any children. Thus, during the 2.5 years we treated her post hysterectomy, she was not interested in freezing eggs for potential fertilization at a later date to be transferred to a gestational carrier.

## Discussion

For many years, case reports were considered the least valuable type of scientific evidence. The emphasis has been on properly designed randomized controlled trials (RCTs). However, RCTs are generally very expensive to conduct, and thus many are sponsored by pharmaceutical companies. Therefore, they are sometimes subject to decisions that are conducive to gaining approval of the drug by governmental agencies. Even surgical trials may prove financially beneficial to the surgeons, if showing a positive benefit or for the institution employing those surgeons. There have been many RCTs involving both standard medical options and surgical options and comparison of laser vs excision surgery for endometriosis and yet there is still no consensus as to what is the proper therapy. Even conclusions from meta-analyses keep changing.

The authors have selected this case to illustrate some of the confusing issues that have not been resolved despite years of studying pelvic pain with or without the presence of endometriosis. In the introduction, it is mentioned that severe pelvic pain may be present despite minimal or no endometriosis present. Yet some women with no pelvic pain undergoing laparoscopic evaluation for infertility may be found to have extensive endometriosis and infertility. In the case presented, she had a long-term history of excruciating pelvic pain, yet only small superficial endometriotic implants present when she finally had a laparoscopy performed.

Thus, this case supports the new concept that pelvic pain is not so much from the presence of inflammatory endometriotic implants but increased pelvic tissue inflammation and pain related to increased cellular permeability and thus infusion of unwanted irritants. Why

does the removal of endometriotic lesions sometimes lead to amelioration of pain and sometimes even for a prolonged period of time? In the case presented, pain relief was only short lived despite the excision technique that was used. Possibly in some cases the presence of endometriosis may exacerbate the permeability defect. One could argue that when no endometriotic lesions are seen or very few superficial implants, the presence of adenomyosis could explain the pain as was the thought of the endometriosis surgeon that the patient consulted. However, in this case she had the hysterectomy, there was no adenomyosis on pathological examination.

The presumptive consideration of adenomyosis by the endometriosis surgery was based on ultrasound findings consistent with the possible presence of endometriosis. Many physicians thinking that pelvic pain equals the presence of endometriosis or adenomyosis will wrongly conclude that if there is no demonstrated presence of endometriosis in a woman with pelvic pain, that pain is probably from adenomyosis and may make wrong decisions for management as the surgeon did in this case. Though this single woman stated she was not interested in having a child, this decision could change in the future, and thus she could be faced with the need for an extremely expensive gestational carrier.

It was mentioned that the one situation where surgery may be preferred over medical therapy may be for infertility since standard medical therapy will preclude pregnancy while the treatment is rendered. Indeed, we have published one of the first studies finding that laparoscopic removal of even mild endometriosis in conjunction with correction of follicular maturation defects, at least in a short period of time, can correct infertility [57]. There is evidence that the pelvic inflammation seen with pelvic pain with or without the presence of endometriosis may be associated with diminished oocyte reserve (DOR) by causing ovarian inflammation and oocyte damage [58].

Surgery could further deplete oocyte reserve by direct damage to the ovaries or damage to ovarian blood supply. In contrast, the use of dopaminergic drugs by impeding inflammatory damage may also impede oocyte depletion [59,60]. In fact, there is some evidence that dopamine agonists could even increase the recruitment of early oocytes that can develop into mature oocytes [61]. The case presented developed severe symptoms of interstitial cystitis shortly after the hysterectomy which was abrogated by resumption of DS. Possibly the interstitial cystitis would have developed subsequent to the severe dysmenorrhea but was precluded by the dopamine agonist therapy [43,44,46].

However, it is known that surgery can cause a subsequent persistent pain syndrome, e.g., chronic regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy. DS has been found to be an effective therapy for CRPS [62]. Thus, another possible reason to avoid surgery and use dopamine agonists for pelvic pain is the possible development of CRPS from the surgical procedure. Finally, the other advantage of treating CPP with dopamine agonists is that this treatment may not only ameliorate the pelvic pain but also improve other medical conditions involving pain in other areas of the body or other medical conditions not always associated with pain e.g., chronic fatigue syndrome which is frequently seen with CPP [63-65].

The pain described in the case report developed interstitial cystitis not only after the removal of just superficial endometriosis implants, but subsequent to hysterectomy. Therefore, there would be no source for more endometrial tissue ectopically implanted from "retrograde reflux" to explain the development of interstitial cystitis. Thus, this case supports the concept that the presence of endometriotic lesions may not be the source of pelvic pain or pelvic pain of bladder region but just a result of the increased tissue permeability which also allows menstrual tissue to traverse mucosal barriers. However, the main cause of pain would be infiltration of inflammatory elements into pelvic tissues. Indeed, there are studies that show that there is at least twice as



much prevalence of interstitial cystitis in patients with endometriosis vs no endometriosis as summarized by Surrey et al [66].

Another condition that is at least 3 times higher in patients with endometriosis compared to the normal population is the irritable bowel syndrome, as summarized by Aldadier et al [67]. We have reported a case where not only did DS eradicate the symptoms of dysmenorrhea, chronic pelvic pain and mittelschmerz but also severe Crohn's disease [47]. Indeed, dopaminergic drugs have provided marked improvement to standard treatment refractory Crohn's disease and ulcerative colitis in patients who did not have severe pelvic pain [68,69]. We have mentioned that CPP can be associated with DOR [58]. Dopamine agonists have also shown great efficacy in treating women without pelvic pain but with DOR present in ameliorating standard treatment refractory ulcerative colitis and Crohn's disease [70,71]. DS has also completely eradicated long-term (20 years) chronic abdominal pain associated with 30 bowel movements daily in a woman with microscopic colitis [72].

On the other end of the spectrum, dopamine agonists have successfully corrected severe constipation in a teenage girl and a woman with DOR [73,74]. A meta-analysis by Columbo et al evaluated 13 different studies. They found a significant increase in migraine headaches in women with endometriosis [75]. We reported a woman who had complete amelioration of not only her dyspareunia and interstitial cystitis following treatment with DS but also her ocular migraines [46]. Dopamine agonists have been very successful in treating treatment refractory headaches from various sources [49,53,54,76-82].

Rheumatoid arthritis has been found to have an increased prevalence in women with endometriosis [83]. DS has been used to effectively treat patients with rheumatoid arthritis refractory to glucocorticoids and tumor necrosis factor alpha inhibitors [84]. There are other comorbidities seen with higher frequency with endometriosis including eczema and urticaria and other dermatologic conditions [85]. Many of these case reports responding to dopamine agonists have been summarized [48,50].

## Conclusion

Though there have been many anecdotal case reports and small series finding that dopamine agonists are frequently quite effective for the relief of pelvic pain of various types with or without the documented evidence of endometriosis. Unfortunately, this treatment is not known by most treating clinicians, most likely because it is not being promoted by pharmaceutical companies. The present case illustrates many of its advantages. 1) The benefit to pain relief is much more prolonged than surgical therapy 2) Pelvic pain is frequently associated with DOR. Surgery may further deplete egg reserve. In contrast, dopamine agonists not only does not cause further egg depletion but may retard the rate of egg loss and possibly even increase the conversion of primordial follicles to primary follicles. 3) In contrast to medical therapy, which prevents pregnancy, dopamine agonists allow the couple to try to conceive while being treated. 4) By diminishing excessive permeability dopamine agonists may actually improve fecundity by inhibiting immune rejection of the early embryo/fetus, thus helping to correct infertility or prevent spontaneous miscarriage. 5) In contrast to surgery or medical therapy, dopamine agonists may also concomitantly correct other co-morbidities that are frequently associated with endometriosis, which are also related to increased cellular permeability.

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