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**Fatima Usmani**  
Senior resident  
Department of Obstetrics  
and Gynaecology  
GSVM, Medical College,  
Kanpur, India

**Amina Usmani**  
Junior resident  
Department of  
ophthalmology, JNMCH,  
Aligarh, India

**Mahmoodullah Raazi**  
Lecturer  
Department of cardiology  
LPS institute of cardiology  
Kanpur, India

**Correspondence:**  
**Fatima Usmani**  
Senior resident  
Department of Obstetrics  
and Gynaecology  
GSVM, Medical College,  
Kanpur, India

## Dopamine agonists in treatment of endometriosis: Are they really effective, a review

**Fatima Usmani, Amina Usmani, Mahmoodullah Raazi**

### Abstract

Endometriosis is a distressing disease, and difficult to treat. Even though it is so common, we still don't know what causes it, and most medications just provide temporary relief. Development and maintenance of endometriotic implants depends on their invasive property and angiogenic potential. Inhibitors of angiogenesis effectively interfere with the maintenance and growth of endometriosis by inhibiting angiogenesis. In vitro studies have shown that dopamine agonists inhibit angiogenesis by reducing levels of VEGF. Small studies have shown their role in endometriosis but further studies especially well-designed RCTs are needed before these novel agents be introduced into clinical stream.

**Keywords:** cabergoline, endometriosis, angiogenesis, dopamine agonists

### Introduction

Endometriosis, pathologically defined as the presence of endometrial like tissue, glands and stroma outside the uterine cavity, is a common, estrogen-dependent disorder associated with pelvic pain and infertility. Its prevalence approaches 14% of the general population, but in women with pelvic pain, infertility or both, the frequency is 35–50%<sup>1</sup>. This disorder is most commonly diagnosed in women of reproductive age, and three main forms have been identified: peritoneal, ovarian and deep endometriosis. Surgery commonly provides temporary relief, although endometriosis is characterized by recurrence in up to 75% of women within 2 years. In addition, surgical removal can be technically challenging and bears the risk of urological and colorectal complications. Medical therapies have traditionally been used to target the estrogen dependency of the disease. They are all effective to a certain extent but are associated with substantial side effects, which limit prolonged exposure, and endometriosis is likely to recur following treatment cessation. For this purpose, key processes in the pathogenesis of endometriosis have been identified, which may serve as potential therapeutic targets.

One of the key processes is angiogenesis, i.e. the development of new blood vessels from pre-existing ones<sup>2</sup>. Angiogenesis is a dynamic process involving many factors. Some pro-angiogenic factors are known to be increased in the peritoneal fluid of women with endometriosis, whereas the levels of others with anti-angiogenic properties are lower<sup>3</sup>. The eutopic endometrium from patients with endometriosis have been shown to exhibit an increased angiogenic potential when compared with healthy women<sup>4</sup>. This may contribute to initiation of disease by retrograde menstruation of highly angiogenic endometrial fragments into the peritoneal cavity. During the last decade, an increasing number of studies have focused on the treatment of endometriotic lesions by application of different anti-angiogenic agents.

Vascular endothelial growth factor (VEGF), a heparin-binding glycoprotein with angiogenic and endothelial cell-specific mitogenic characteristics, and with vascular permeability properties, is considered to play a pivotal role in both physiologic and pathologic angiogenesis<sup>5</sup>. VEGF has been shown to be released by macrophages present in increased amounts in the peritoneal fluid of women with endometriosis<sup>6</sup>. Moreover, there is a positive correlation between the severity of the disease and the secretion of VEGF in peritoneal fluid<sup>7</sup>. The expression of VEGF is increased in active red lesions<sup>8</sup> and deep infiltrating endometriosis<sup>9</sup>. Binding of VEGF to its type-2 receptor (VEGFR-2) appears to be the main regulator of vasculogenesis, angiogenesis and vascular permeability<sup>10</sup>.

To demonstrate the role of VEGF in endometriosis-related angiogenesis, experiments were performed with VEGF ligands and VEGFR-2 blocking antibodies. Hull et al. (2003) employed a soluble truncated receptor that antagonizes VEGF, and also anti-VEGF-A antibodies.

In both cases, they reported a significant decrease of endometriotic implants and vascular destruction<sup>11</sup>. Nap et al. (2004) employed several anti-angiogenic agents to inhibit endometriosis lesions in nude mice<sup>12</sup>. A specific VEGF-A inhibitor (Avastin) and other angiogenesis inhibitors (TNP-470, Endostatin, Anginex) were found to significantly decrease endometriosis lesions and the presence of blood vessels. Similarly, Park et al. reported the inhibition of endometriosis development in Rhesus monkeys by blocking the VEGF receptor<sup>13</sup>.

We focused our attention on the dopamine/dopamine receptor 2 pathway, whose activation is involved in the regulation of angiogenic events<sup>14</sup>, mediated by VEGF/VEGFR-2 signalling<sup>15</sup>.

A decade ago, Basu et al (2001) made interesting discovery that the neurotransmitter dopamine selectively inhibits the vascular permeabilizing and angiogenic effect of VEGF at nontoxic levels, revealing a new link between the nervous system and angiogenesis. This led to the idea to use dopamine agonists for anti-angiogenic therapy<sup>16</sup>. Novella-Maestre et al analysed the effect of cabergoline on growth and vascularisation of endometriotic lesions in the nude mouse model. They found that daily oral treatment with cabergoline over 14 days causes regression of endometriotic lesions by suppression of cell proliferation and VEGF mediated angiogenesis. They could further demonstrate that cabergoline treatment results in significantly lower expression of VEGF and VEGFR-2 in endometriotic lesions. Thus they concluded that dopamine agonists may be successful in the treatment of peritoneal endometriosis<sup>17</sup>. However, chronic cabergoline treatment is known to be associated with an increased incidence of cardiac valve regurgitation<sup>18</sup>. Delgado-Rosas et al compared the efficacy of non-ergot derived dopamine agonist quinagolide with that of cabergoline and found both to be equally effective in inhibiting angiogenesis and vascularization of endometriotic lesions<sup>19</sup>. Gomez et al. found 70% reduction of endometriotic lesions with quinagolide, with 35% vanishing completely<sup>20</sup>. Further histological studies revealed that this was associated with downregulation of VEGF/VEGFR-2, pro-angiogenic cytokines and plasminogen activator inhibitor-1 within the lesions. Hamid et al did a small study and showed that cabergoline was slightly more effective in reducing the size of endometrioma as compared to the standard treatment which uses GnRH agonist injections<sup>21</sup>.

Most of women suffering from endometriosis are young in reproductive age group and physiological angiogenesis is a major prerequisite for reproductive function<sup>22</sup>, antiangiogenic agents have to target specifically angiogenesis in endometriotic lesions or, at least, should not exert long term side effects on blood vessel development within the ovary and uterus after stopping treatment. Moreover, because anti-angiogenic therapy carries a risk of impairing fertility, they can be used primarily in patients suffering from severe pain associated with endometriosis. For this reason those agents having favourable risk profile and approved for use of other benign disease be preferred.

The recommended dose is 0.5 mg twice weekly at least for three months. Cabergoline can be used preoperatively, postoperatively, alone or in combination with COCs. We can use cabergoline alone in those patients who desire fertility at the same time and this is a clear cut advantage over other forms of therapies available, all of them delay conception by their mechanism of actions and they usually don't give pain relief while dopamine agonist through their action on nerve fibres decrease the pain as well. No adjuvant therapy is

needed as it does not bring hypoestrogenic and bone density changes in these patients<sup>23</sup>.

Cabergoline is effective in endometriotic patients with elevated prolactin levels. In patients with normal prolactin levels but presenting with galactorrhoea and infertility cabergoline does affect the outcome favourably. The study of patients with OHSS, who were given cabergoline, disease process could be halted in dose dependent manner without affecting the implantation and growth of embryo and this point goes indirectly in favour of its use in these patients. Side effects are well tolerated and in a recent study done by Herring and colleagues they concluded that the incidence of valvular heart disease was not greater in these patients who were taking cabergoline for years in these patients who were taking cabergoline for years in the dose prescribed for prolactinomas. Importantly, Cabergoline treatment during pregnancy does not increase the risk of spontaneous miscarriage, premature delivery or congenital abnormalities.

**Conclusion:** A comprehensive synthesis of the complex pathogenesis of endometriosis remains elusive, but it is clear that it is a multifactorial disease and development and maintenance of endometriotic implants depend on their invasive capacity and angiogenic potential. This angiogenic potential has been viewed and targeted as a potential new target for future therapeutic interventions but further studies especially well designed RCTs are needed before these novel agents like cabergoline can be introduced into main clinical stream.

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