ORIGINAL ARTICLE

A Comprehensive Review of the Efficacy and Safety of Dopamine Agonists for Women with Endometriosis-associated Infertility from Inception to July 31, 2022

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ABSTRACT

Background. Current medical management of endometriosis leads to suppression of ovulation and will not be helpful for women with endometriosis who are desirous of pregnancy. Thus, drugs that can both treat endometriosis and its associated infertility are highly warranted.

Objective. Anti-angiogenic agents are potential drugs for patients with endometriosis and infertility. Among these drugs, dopamine agonist (DA) is promising since it does not interfere with ovulation, is safe, and not teratogenic. The aim of the study is to determine the efficacy and safety of DA for improving reproductive outcomes in women with endometriosis and infertility.

Methods. A qualitative narrative review was done from inception to July 31, 2022 using the appropriate MeSH terms in PubMed, Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, ClinicalTrial.gov, and World Health Organization International Clinical Trials Registry Platform. Date analysis was through qualitative analysis and synthesis of researches and their outcome measures.

Results. No studies used the core outcomes for trials evaluating treatments for infertility associated with endometriosis. All the included articles in the review supported the possible anti-angiogenic effects of DA on the vascular endothelial growth factor [VEGF] /VEGF receptor system. The use of DA does not have an effect on ovulation and menstrual cyclicity. Studies on safety profile of DA were consistent with existing data.

Conclusion. Most of studies reviewed demonstrated that DA were effective in reducing endometriotic lesions. However, further research is required to establish whether this anti-angiogenic effect can improve reproductive outcomes in women with endometriosis-associated infertility.

Keywords: endometriosis, dopamine agonists, infertility, angiogenesis inducing agents, anti-angiogenesis effects

eISSN 2094-9278 (Online)
Published: June 14, 2024
https://doi.org/10.47895/amp.vi0.6994

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INTRODUCTION

Description of the condition

Endometriosis is defined as a disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium.[1-3] The ectopic endometrial tissue grows under the cyclic influence of ovarian hormones, most specially estrogen.[4]

Endometriosis is estimated to affect 10% of the reproductive aged-female population.[5,6] A patient with endometriosis is usually in her child-bearing age, who has symptoms of dysmenorrhea, pelvic pain, and difficulty in conceiving. Almost a quarter to half of infertile women have

endometriosis.[7] A third to half of women with endometriosis are infertile.[8,9] Infertile women are significantly associated with moderate to severe endometriosis than previously fertile women.[10] About 17%–44% of patients with endometriosis have endometriomas.[11]

The probability of achieving a live birth in a single cycle or fecundity is 0.15 to 0.20 per month and decreases with increasing age. A lower monthly fecundity of about 0.02–0.1 per month was observed in women with endometriosis.[12,13] In addition, endometriosis is associated with a lower live birth rate; with the advanced stages of endometriosis being associated with lower live birth rate.[14]

The mechanisms of the pathophysiology of infertility in women with endometriosis are not yet fully understood and may be multifactorial.[7,15,16] At present, the most popular still is the classical theory of Sampson on retrograde menstruation.[17] This phenomenon has been subsequently explained as the shedding of viable endometrial-based adult stem cells and mesenchymal cells which attach to the pelvic peritoneum and grow as homologous grafts under cyclic estrogenic influence.[18]

The ectopic endometrial cells adhere to the extracellular matrix[19-21] invade the matrix through the metalloprotease [MMPs],[21] grow through the growth factors, steroid hormones, and k-ras mutations and survive through angiogenesis and resistance to apoptosis,[22] and induction of local immunosuppression in the peritoneum. These events activate wound healing processes that can lead to fibrosis, scarring, and adhesion formation. In addition, there is activation of the inflammatory and immune mechanisms that could stimulate further growth of the ectopic endometrial cells.[23] Figure 1 shows how the resulting anatomical abnormalities including peri-tubal and peri-ovarian adhesions and pelvic distortion can explain the infertility in advanced stages of endometriosis which can impair tubal motility, oocyte release/pick up, hinder sperm transport and motility, and compromise fertilization and embryo transport.[24-27] Thus, the processes prior to scarring, fibrosis, and adhesion formation have been studied as targets for the management of endometriosis-related infertility to prevent the progression of the disease.

Three of the prerequisites for growth of endometriosis are angiogenesis, vasculogenesis, and inosculation.[28-30] All three are involved in vascularization which is very important in the progression and maintenance of the ectopic endometriotic lesions. When there is low oxygen supply,[30,31] angiogenesis or the growth or sprouting of new blood vessels from pre-formed blood vessels[32-35] is stimulated and maintained by vasculogenesis where circulating endothelial progenitor cells from the bone marrow are added into the de novo formation of microvascular endothelium.[30,33,36-39] Inosculation or union of the pre-existing microvessels in the exfoliated endometrial tissues with the surrounding host blood supply will establish the microvasculature in the ectopic tissues.[30,40] As a consequence, the growth and survival of endometriotic lesions is crucially dependent on the establishment of an adequate blood supply[41,42] which is comparable to tumors and their metastases.[43]

The classical approaches in the management of endometriosis can be pharmacological, surgical or both.[7,44-51]

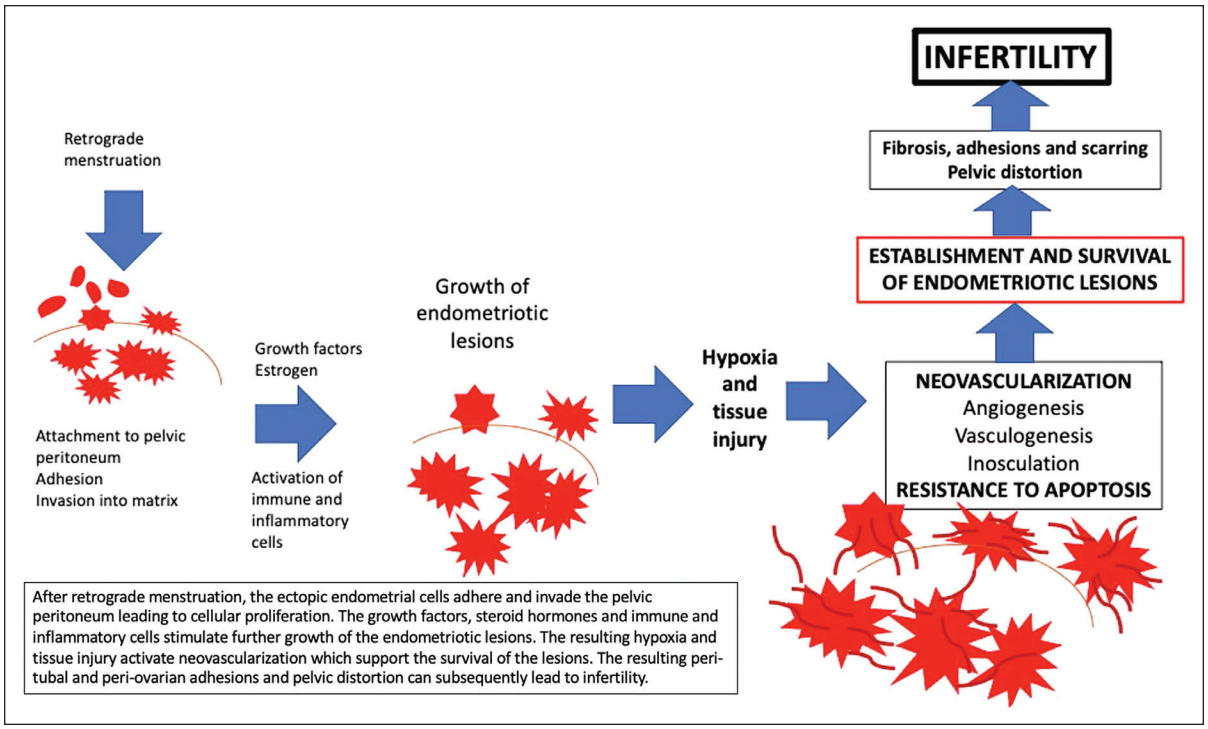


Figure 1. Proposed mechanism of the pathophysiology of endometriosis-associated infertility.

Pharmacological treatment provides symptom-relief (pelvic pain, dysmenorrhea, dyspareunia) by suppression of endogenous estrogen production with gonadotropin-releasing hormone agonists, progestins, combination oral contraceptives, androgenic agents (danazol).[51-55] However, a Cochrane review of 25 trials using progestins, danazol, oral contraceptives and gonadotropin-releasing hormone (GnRH) agonists for ovulation suppression showed no benefit in the treatment of endometriosis-related infertility.[56]

Surgical management of endometriosis may be conservative involving resection of endometriotic implants, adhesiolysis, and restoration of normal pelvic anatomy, and definitive which includes removal of the uterus, ovaries, and all visible endometriotic lesions.[7] Although the surgery for endometriosis-related infertility will definitely be the conservative approach for minimal to severe disease, there is inevitable ovarian injury during the resection of endometriotic lesions.[57] This may lead to the reduction in the ovarian reserve which may already be decreased secondary to the presence of endometriosis itself.[11,57,58] Furthermore, the recurrence rates after surgery can range from 6 to 67% depending on the criteria used.[59-63]

Therefore, with the undesirable ovulation suppression and hypoestrogenic side effects of medical management, the risks of complications, reduction of ovarian reserve in surgical treatment and the risk of recurrence, newer drugs need to be developed for endometriosis-associated infertility, which will not inhibit ovulation and/or which can decrease existing or prevent the growth of new endometriotic lesions. A potential therapeutic target for these drugs will be angiogenesis[31,64-66] which is a pivotal step in the formation of endometriosis. Stopping the growth of new blood vessels could stop the growth of new lesions and atrophy of older ones.

A systematic overview of experimental studies, both in-vivo and in-vitro, of various anti-angiogenic agents demonstrated that reducing blood supply leads to regression of endometriotic lesions, without affecting the ovarian function.[67]

Among the different anti-angiogenic compounds, dopamine agonists [DRD2-A][68] have been used clinically and safely with tolerable side effects. They do not appear to inhibit the physiological angiogenesis in reproductive organs[69,70] and do not affect fertility or pregnancy in young women[30,71,72].

Description of the intervention

DRD2-A act through the D2 subtype of dopamine receptors [DRD2]. Ergot-derived DRD2-A, bromocriptine, cabergoline, and pergolide have the highest selectivity for the pituitary dopamine receptors and compete for binding to these sites with dopamine itself. The non-ergot derived agent, Quinagolide, has a comparably high D2 receptor binding affinity.[73]

DRD2-A have been used in humans for the treatment of hyperprolactinemia considering that dopamine inhibit prolactin production.[74-77] They decrease the size of the pituitary prolactin-secreting tumors, reduce circulating prolactin levels, and resume ovulation in approximately 70% of women with microadenomas and 30% of women with macroadenomas.[73] Recently, they appear to lower the incidence of moderate or severe ovarian hyperstimulation syndrome [OHSS] in women at high risk of OHSS.[78-83] They are also indicated in Parkinson's disease to enhance motor function and reduce levodopa requirement.[84-86]

Some of the side effects of DRD2-A include nausea, headache, light-headedness, orthostatic hypotension, fatigue, and sometimes psychiatric symptoms.[73,87] Nausea occurs less with cabergoline treatment than in bromocriptine[73,76] or by using the vaginal administration of bromocriptine[88]. There was no increase in the risk of spontaneous miscarriage, premature delivery or congenital abnormalities with the use of cabergoline during pregnancy.[69,71,89]

How intervention may work

Out of the three prerequisites for the growth of endometriosis, most of the studies in the field of endometriosis research have been on angiogenesis.[30] Among the different angiogenic factors, VEGF has been recognized as the prototypic and principal regulator of physiologic and pathologic angiogenesis.[33,90-92] VEGF is a member of a family of heparin-binding, endothelial-specific proteins, which signals many cells to stimulate the formation and growth of blood vessels in response to exercise, altered hormonal milieu,[93-95] injury or hypoxic conditions[31,40,96,97]. It is initially known as vascular permeability factor [VPF] since it increases capillary permeability.[98]

All members of the VEGF family bind to tyrosine kinase VEGF-receptors, the VEFGRs on the cell surface, especially Flt-1 and KDR resulting to the dimer formation, autophosphorylation, and stimulation of mitogen-activated protein kinases.[92,99] VEFGR-1 is important for hematopoietic cell development. VEFGR-2 is for vascular endothelial cell development. VEFGR-3 is for lymphatic endothelial cell development.[99] The binding of VEGF to VEGFR-2 receptor is the critical regulator of the processes of vasculogenesis, angiogenesis, and capillary permeability.[100]

In women with moderate to severe endometriosis, higher peritoneal levels of VEGF were observed compared to women without the disease.[101-106] The endometriotic lesions with high proliferative activity had higher microvessel density, higher vascular expression of VEGFR-2, and higher levels of VEGF-A in peritoneal fluid and serum than those lesions with low proliferative activity.[104] The activated macrophages can also secrete VEGF which is controlled directly by ovarian steroids.[107] Targeting VEGF can possibly lead to prevention and growth of endometriosis.

It was only more than two decades ago that the link between the nervous system and angiogenesis was discovered by Basu et al.[108] They found out that the non-toxic levels of dopamine selectively inhibit the vascular permeability and angiogenic activities of VPF/VEGF. The binding of

dopamine to the DRD2 trigger endocytosis of VEGFR 2, which is critical for promoting angiogenesis. This resulted to prevention of VPF/VEGF binding, receptor phosphorylation, and subsequent signaling steps inhibiting pathologic angiogenesis in tumors.[108-110] (Figure 2)

Why the review is important to do

The current medical management of endometriosis leads to suppression of ovulation and will not be helpful for women with endometriosis who are desirous of pregnancy. Thus, drugs that can both treat endometriosis and its associated infertility are highly warranted. Improving the management of endometriosis is consistent with the Sustainable Development Goal (SDG) 3 on good health and well-being set by the United Nations General Assembly in 2015.

The antiangiogenic agents have been considered as potential new targets since angiogenesis is a crucial step in the pathogenesis of endometriosis. Among these drugs, DRD2-A are quite promising since aside from not interfering with normal ovulation, their safety profile are more acceptable and they are not teratogenic.

Therefore, the aim of the study was to determine the efficacy and safety of DRD2-A for improving reproductive outcomes in women with endometriosis and infertility. Specifically, to determine the efficacy and safety of DRD2-A in both pre-clinical studies and clinical studies in women with endometriosis and infertility.

METHODS

Study design

The study did a qualitative narrative review of published data.

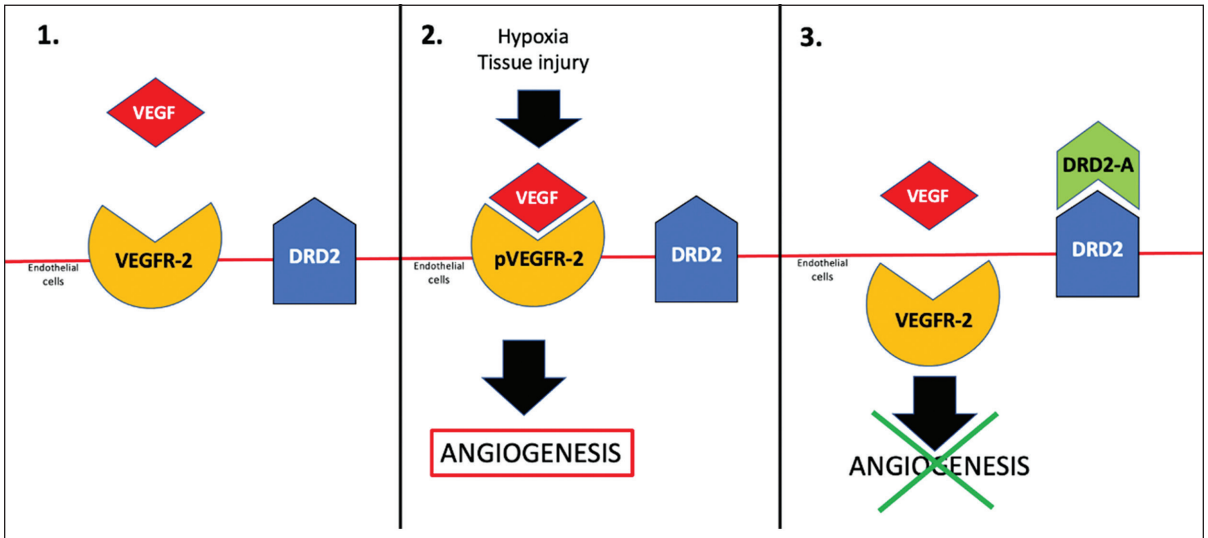
Search strategy

Only online search for literature from inception to July 31, 2022 was performed. The key words 'endometriosis' and 'ectopic endometrium' were paired with the key words 'dopamine agonists', 'infertility', 'cabergoline', 'quinagolide', 'bromocriptine', 'angiogenesis', 'vascularization', and 'anti-angiogenesis'.

Articles were identified through the following electronic databases: PubMed, Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (CENTRAL). Registers of ongoing trials and all reference lists of included trials in ClinicalTrial.gov (www.clinicaltrials.gov) and World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) were also included. All relevant articles were examined and their reference lists were reviewed in order to identify other studies for possible inclusion in this review. The assessment of the full text journals for eligibility was done by the author only and the assessment of the risk of bias of the studies included was not performed which were the delimitations of this review.

Selection criteria

All studies, both preclinical and clinical, on the use of DRD2-A for endometriosis or endometrioma associated with



1. VEGFR-2 and DRD2 are present in the endothelial cells. 2. In the presence of hypoxia or tissue injury, VEGF secretion will be increased and binding of VEGF to VEGFR-2 leads to phosphorylation of VEGFR-2 which is a critical step in angiogenesis. 3. Binding of DRD2-A in DRD2 will cause internalization of the VEGFR2 preventing the binding to and phosphorylation of VEGFR2, thus inhibiting angiogenesis. VEGF – vascular endothelial growth factor; VEGFR2 – VEGF receptor type 2; dopamine agonist type 2 receptor; pVEGFR2-phosphorylated VEGFR2 and DRD2 – DRD2-A – dopamine agonist.

Figure 2. How dopamine agonist may work.

infertility and/or angiogenesis were included. The abstracts of studies identified in the search were reviewed to exclude irrelevant or repeat/double citations. (Table 1)

Types of outcome measures

1. For determining efficacy of DRD2-A in pre-clinical studies, Table 2 shows the outcome measured to assess the anti-angiogenic effects of dopamine agonists.
2. For determining the efficacy of DRD2-A in clinical studies, the outcomes were divided into three: a) outcomes to determine anti-angiogenic effects, b) outcomes to determine effect on ovulation and menstrual cyclicity, and c) outcomes identified for trials evaluating potential treatments for infertility associated with endometriosis,[111] known as the core outcome set.
3. For determining the safety of DRD2-A for women with endometriosis and infertility, the adverse events from dopamine agonist use were the outcome measured, which was one of the core outcomes identified by Duffy et al.[111]

Data analysis

Date analysis was through qualitative analysis and synthesis of researches and their outcome measures.

RESULTS

The initial search yielded 188 studies (Figure 3). On further review of the titles, abstracts, and full text articles, and

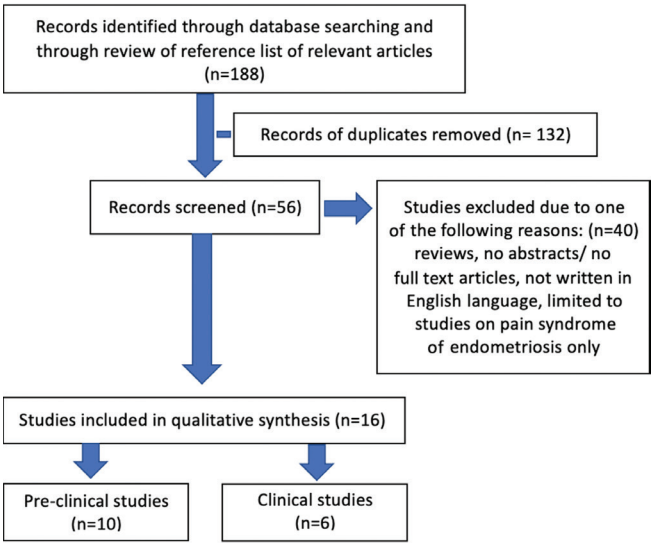


Figure 3. Results of the search strategy of published data.

Table 1. Inclusion and Exclusion Criteria for Studies on the Use of Dopamine Agonists in Endometriosis-associated Infertility in the Present Review

Inclusion criteria	Exclusion criteria
• Randomized controlled trials, observational studies, case reports and proceedings of scientific meetings • Written in English language • All electronically listed publications in PubMed, Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (CENTRAL) until December 18, 2021 • Studies on the use of dopamine agonists for endometriosis/ endometrioma and/or infertility and/or angiogenesis • Animal and human studies, in-vitro and in-vivo	• Editorials, letters to the editor, reviews, abstracts, duplicate papers • Written in a language other than English • All electronically listed publications in PubMed, Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (CENTRAL) after December 18, 2021 • Studies on the use of dopamine agonists for endometriosis and related pain syndrome with outcome measures limited to pain measurements/scores

Table 2. Outcomes Measured to Assess Efficacy and Safety of Dopamine Agonists for Endometriosis-associated Infertility

Outcome measures	Efficacy				Safety
	Pre-clinical studies	Clinical studies			
	To determine anti-angiogenic effects	*To determine anti-angiogenic effects*	*To determine effect on ovulation and menstrual cyclicity*	*To evaluate potential treatments for infertility-associated endometriosis**	
Primary outcomes	Reduction of endometriotic lesions	Reduction of endometriotic lesions		Live birth rate	Adverse events*
Secondary outcomes	1. Cellular proliferation index 2. Neoangiogenesis 3. VEGF expression 4. VEGF receptor (KDR) expression / phosphorylation 5. Angiogenic expression	1. Cellular proliferation index 2. Neoangiogenesis 3. VEGF expression 4. VEGF receptor (KDR) expression / phosphorylation 5. Angiogenic expression	1. Ovulation 2. Menstrual cyclicity 3. Reproductive hormone levels (FSH, LH, estradiol and progesterone in early follicular or mid-luteal phase) 4. Endometrial histology	1. Clinical pregnancy* 2. Multiple birth rate* 3. Ectopic pregnancy * Miscarriage* 4. Stillbirth* 5. Time to pregnancy leading to live birth* 6. Gestational age at delivery* 7. Birthweight* 8. Neonatal mortality* 9. Major congenital abnormalities* 10. Recurrence rate of endometriosis* 11. Patient satisfaction with treatment*	

**Core outcome set by Duffy et al., 2020[112] (Appendix)*

exclusion of double citations, there were only sixteen studies which fit the inclusion criteria. Ten of the sixteen studies were pre-clinical studies (Table 3). Six were clinical studies (Table 4).

Efficacy of DRD2-A in endometriosis and infertility in pre-clinical studies

Endometriotic lesions after DRD2-A treatment

There were 10 pre-clinical studies which determined the anti-angiogenic effect of dopamine agonists on endometriosis. Out of the 10, eight studies[68,112-118] investigated the primary outcome on reduction of endometriotic lesions after DRD2 treatment. Six out of the eight studies[112-115,117,118] showed significant decrease in the endometriotic lesion size. Although, there was no significant decrease in the lesion size in the study by Novella-Maestre et al.,[68] it showed that it significantly reduced the percentage of active lesions which was one of the findings also by Delgado-Rosas et al.[112] The other study which showed no reduction in the lesion was the recent study by Karslioglu et al.[116]

Cellular proliferation after DRD2-A treatment

There were 2 studies[68,112] which showed reduced cellular proliferation of endometriotic cells using Ki-67 labelling index, where the total antigen expression per square micrometer (proliferation index) was quantified by morphometric analysis.

Neoangiogenesis after DRD2-A treatment

There were four studies[68,112,118,119] on neoangiogenesis. All four studies showed significantly decreased immature blood vessels in the DRD2-A treatment groups. The three studies[68,112,119] showed no significant decrease in the microvascular density. However, Tejada et al.[118] observed that vascular density was significantly lower in DRD2-A and anti-VEGF groups when compared to control and that the percentage of mature vasculature was significantly decreased in the control.

Table 3. Pre-clinical Studies Focusing on the Anti-angiogenic Effects of Dopamine Agonists on Endometriosis

Author, year	Medications	Treatment timing	Species or cell culture/tissue type/ transplantation site	Outcomes	Other findings
Novella-Maestre et al., 2009[68]	Cb2 0.05 mg/kg/day (low dose) Cb2 0.1 mg/kg/day (high dose) vehicle solution (1:6 alcohol in sterile water mixture) administered orally for 14 days	Three weeks after establishment of lesions	Nude mice /human endometrium/ peritoneal cavity	1. Significantly reduced (p=0.05) percentage of recovered active lesions when low- (58.6+9.7%) or high- (60.4+ 8.4%) dose Cb2 was employed as compared with the controls (89.6 + 5.7%). 2. Significant difference (P, 0.001) among the groups with respect to the newly formed and mature blood vessel 3. No statistical difference among the groups in the vessel density 4. Significantly lower (p <0.05) VEGF expression in Cb2-treated groups 5. Decrease total VEGFR-2 and pVEGFR-2 staining in blood vessels of the Cb2-treated groups	Up-regulation of anti-angiogenic gene Ang-1 (p <0.05) and Wnt-1 and suppression of pro-angiogenic Notch-4 expression
Novella-Maestre et al., 2010[120]	Cb2 0.05mg/kg/day (low dose) Cb2 0.1mg/kg/day (high dose) vehicle solution (1:6 alcohol in sterile water mixture) administered orally for 14 days	Three weeks after establishment of lesions	Nude mice/human endometrium/ peritoneal cavity	1. Significantly lower VEGF gene and protein expression in Cb2-treated groups 2. Significantly decreased VEGFR2 (KDR) protein expression	There is DRD2 expression in all 3 groups of endometriotic lesions; with significantly higher expression of VEGF in patients with mild and severe endometriosis compared with healthy patients
Delgado-Rosas et al., 2011[112]	Quin 50ug/kg/day Quin 200ug/kg per day Cb2 50mg/kg/day Vehicle administered orally for 14 days	Three weeks after establishment of lesions	Mice model by transplantation of uterine horn to the peritoneum	1. Decreased percentage of active lesions and lesion size in both DRD2-A-treated groups when compared with controls. 2. Reduced proliferation of endometrial implants with Cb2 (P=0.020) and the 50 mg/kg (P=0.029) and 200 mg/kg (P=0.039) quinagolide groups with respect to controls 3. Significant decrease in the number of immature vessels remaining in the DRD2-A-administered groups. 4. No decrease in MVD 5. Significantly lower VEGF mRNA levels in the quinagolide- but not in the Cb2-treated groups with respect to controls 6. Significant decreased in VEGFR 2 mRNA in all DRD2-A treated groups	Cabergoline and quinagolide, equal effect in reducing endometriotic lesions as antiangiogenic agents.

Table 3. Pre-clinical Studies Focusing on the Anti-angiogenic Effects of Dopamine Agonists on Endometriosis *(continued)*

Author, year	Medications	Treatment timing	Species or cell culture/tissue type/ transplantation site	Outcomes	Other findings
Novella-Maestre et al., 2012[119]	Cb2 0.05mg/kg/day (low dose) Cb2 0.1mg/kg/day (high dose) administered orally for 14 days	Three weeks after establishment of lesions	Nude mice/human endometrium/ peritoneal cavity	1. Significantly decreased (P<.001) immature blood vessel in Cb2-treated lesions in comparison with control (6.9 ± 2.1) 2. No statistically significant differences were found among the groups for MVD (p=.1391)	Significant decreased in nerve fiber density and number of macrophages and mast cells in the Cb2-treated group when compared with controls.
Ercan et al., 2015[113]	Group 1 injected single dose of Leuprolide Acetate 1 mg/kg SC Group 2 Bromocriptine 1 mg/kg/day orally for 30 days Group 3 Cb2 0.1 mg/kg/day orally for 30 days Group 4 control (1 ml saline solution SC	3 days after establishment of lesions OR 31 days after implantation surgery	Wistar rat/ autologous endometrium/ peritoneum[121]	1. Significant reduction in all treatment groups 2. Highest reduction in endometriotic implant sizes in group 1 (from 21.75 ± 3.74 to 7.58 ± 4.03 mm^2, p:0.002), followed by group 2 (from 20.33 ± 3.84 to 9.41 ± 4.83 mm^2, p:0.002), then group 3 (from 20.83 ± 3.97 to 10.41 ± 3.17 mm^2, p:0.002)	Cabergoline and bromocriptine, comparable to GnRH agonist in reducing endometriotic lesion.
Akyol et al., 2016[114]	Quin 200 ug/kg/day Control saline 0.1ml/day by oral gavage for 4 weeks	1 day after the establishment of the lesions OR 29 days after implantation surgery	Wistar rat/autologous endometrial tissue/ peritoneum[122]	1. Significant reduction in volume after Quin (p=0.010) 2. Significant reduction in levels of VEGF in peritoneal samples in Quin-treated rats (p=<.010)	Significantly reduced levels of interleukin 6 peritoneal samples in quinagolide-treated rats p=0.03)
Barbe et al., 2019[115]	Cb2 0.075 mg/kg body weight daily SC Celecoxib 30 mg/kg + Cb2 0.075 mg/kg Celecoxib 30 mg/kg Control group	8th day after implantation surgery	Rattus Norvegicus Wistar/autologous uterine fragments/ peritoneum	1. Reduction of volume of almost 9 times in Cb2 treated group than that in the control group. 2. No potentiation or summation of their effects in the combination of Cb2 and Celecoxib 3. Significantly lower efficacy of Celecoxib than Cb2	
Karslioglu et al., 2021[116]	Cb2 0.1 mg/kg/day Micronized progesterone (MP) 2.5 mg/kg/day Placebo administered orally for 4 weeks	8 weeks after implantation surgery	Sprague Dawley rat/ autologous endometrial tissue/ peritoneum	1. No significant difference in implant size volume before and after treatment	
Keles et al., 2021[117]	Cb2 – Cb2 0.1 mg/kg/ day PO E – E 2 mg/ kg SC 3x/week E + Cb2 - E 2 mg/kg SC 3x/ week PLUS Cb2 0.1 mg/kg/ day PO Sh - saline 2 ml / kg/ day SC All treatment were given for 2 weeks Control I	5 days after establishment of lesions OR 33 days after implantation surgery	Wistar albino rat/ autologous endometrial tissue/ peritoneum	1. Significant reduction in implant size all treatment groups (p<0.05). 2. Highest decrease of endometriotic implant in volume in E group, followed by E + Cb2, then Cb2 group. 3. Significant decreased VEGF staining in ectopic endometrium (p<0.001) in all treatment groups	Significantly decreased TNF-α staining in the ovary in E and E + Cb2 groups comparing to Sh, Co, and Cb2 groups (p<0.05).
Tejada et al., 2021[118]	Cb2 50 µg/kg by oral gavage, every 3 days CBO-P11 (anti-VEGF) daily intraperitoneal administration of 0.6 mg/kg Control group with 100 µl of 5% glucosaline vehicle orally.	5 days after implantation surgery	Nude mice/human endometrium/ peritoneum	1. Comparable significant reduction in lesion size in Cb2 and anti-VEGF groups when compared to control. 2. Scarce immature vessels in lesions in treated groups 3. significantly lower percentage of mature vasculature in the control group, 40% (p<0.001) compared to the 90% and 76% values observed in the anti-VEGF and Cb2 treated group 4. Significant reduction in vascular density in the Cb2 (29.7%) and anti-VEGF (34.3%) treated groups vs. control (p < 0.05)	Similar extent of antiangiogenic effects for anti-VEGF and Cb2 group in which suggest that Cb2 is a powerful VEGF/ VEGFR2 inhibitor in decreasing vascularization and lesion size

Cb2- Cabergoline; VEGF- Vascular endothelial growth factor; VEGFR; Vascular endothelial growth factor receptor; KDR- VEGFR 2 receptor; DRD2 – dopamine agonist type 2 receptor; DRD2-A- dopamine agonist; Quin- Quinagolide; MVD- mean vascular density; SC – subcutaneous; PO- orally; E- etanercept

Gene and protein expression of VEGF after DRD2-A treatment

The four studies[68,114,117,120] demonstrated significantly lower VEGF expression. A single study[120] showed significantly reduced VEGF gene expression and one study[112] detected lower VEGF mRNA levels in the quinagolide group but not in the cabergoline-treated group.

Gene and protein expression of VEGFR-2 (KDR) after DRD2-A treatment

Two studies[68,120] observed significantly decreased VEFGR-2 (KDR) expression. One study[68] detected significantly reduced VEGFR-2 phosphorylation. A significant decrease in the VEGFR-2 mRNA was seen in the Delgado-Rosas et al. study.[112] Table 3 summarizes the pre-clinical studies on the efficacy of dopamine agonists as anti-angiogenic agent in endometriosis.

Table 4. Clinical Studies Focusing on the Efficacy and Safety of Dopamine Agonists on Endometriosis

Author, year	Experimental drug / Control drug	Type of study (n)	Patients	Outcomes of efficacy	Other findings / remarks	Outcomes for safety
Gomez et al., 2011[123]	Quinagolide, titrated from 25 mg/d to 75 mg/d during the 18–20 treatment period	Proof of concept study (n=9)	Hyper-prolactinemic patients with endometriosis	1. 69.5% reduction in the size of the lesions, with 35% vanishing completely 2. No difference in cell proliferation 3. No difference in quantity of immature vessels and vascular density 4. Reduction of the density of VEGFR2 by twofold 5. Reduction in phosphorylation of VEGFR2-Tyr 951 by almost 50%	Downregulation of three proangiogenic cytokines (CCL2, RUNX1, and AGGF1) and plasminogen activator inhibitor (PAI)	No major complications
Iraci Sareri et al., 2012[126]	Group A (n=8) 0.25 mg of Cabergoline three times a week Group B (n=8) placebo	Randomized placebo study (n=16)	Women with diagnosis of endometriosis	1. Decrease in cellular proliferation index compared to control. 2. Decrease in neoangiogenesis than control. 3. Decrease in VEGFR2 phosphorylation than control.		
Hamid et al., 2014[124]	Group I – (n=71) cabergoline tablets, 0.5 mg tablets, twice per week for 12 weeks. Group II (n= 69) LHRH agonist, decapeptyl, 3.75 mg subcutaneous, single injection, once/month for 3 months	Prospective randomized study (n=140)	Patients complaining of endometrioma	1. Significant decrease (64.7%) in the mean endometrioma diameter in group I 2. 21.7% decrease in the mean endometrioma in group II		Minimal side effects
Bagger and Arce, 2020[128]	Quinagolide vaginal rings with target release rates of 4.5 and 13.5 mg/day, administered for two consecutive menstrual cycles	Clinical phase 1 trial - randomized double-blind study (n=134)	Female healthy volunteers	1. Ovulation not affected, with confirmed presence of corpus luteum in 93% of the women after two cycles 2. No changes in menstrual cycle duration (median 25.5- 28.0 days), bleeding duration (median 4.0-5.0 days), or mid-luteal phase 3. No impact on serum FSH, LH, estradiol and progesterone levels in the early follicular or mid-luteal phases 4. Endometrial histology (all secretory) with quinagolide vaginal ring at any of the release rates		Well tolerated
Shume et al., 2021[125]	Cabergoline, 0.5 mg tablet twice weekly, was given to 28 women for 3 months. Dienogest, 2 mg tablet daily, was given to 28 women for 3 months	Prospective comparative study (n=56)	Women with endometrioma (diagnosed by ultrasound)	1. Non-significant percentage reduction in endometrioma size in women in both treatment groups		No significant difference in the incidence of nausea, vomiting, headache, and abnormal uterine bleeding between cabergoline and dienogest groups
DiVasta et al., 2021[127]	Group 1 (n=3) received 5 mg of oral norethindrone acetate (NETA) daily plus placebo tablet twice weekly. Group 2 (4=4) received oral 0.5 mg of cabergoline twice weekly plus placebo tablet daily	Randomized, double-blind, placebo-controlled pilot study (n = 9)	Women with surgically confirmed endometriosis.	1. Lower serum VEGF concentrations		Well-tolerated. No serious adverse events

Efficacy of DRD2-A in endometriosis and infertility in clinical studies

Angiogenesis after DRD2-A treatment

There were five studies on the possible anti-angiogenic effect of dopamine agonists. Three studies[123-125] were on the significant reduction of endometriotic lesions/cysts. Two studies[123,126] on cellular proliferation showed inconsistent findings; one showed no difference in cellular proliferation[123] and the other study[126] showed a decrease in cellular proliferation index when compared with the control. The effects on neoangiogenesis were also not similar in both studies.[123,126] One study[127] observed reduction in VEGF levels after treatment. One study[123] demonstrated lower levels of VEGFR 2 and two studies[123,126] detected less VEGFR-phosphorylation.

Effect on ovulation, menstrual cyclicity, reproductive hormones, and endometrial histology after DRD2-A treatment

There was one randomized, double blind study[128] which evaluated in 28 regularly menstruating healthy women the effect of quinagolide extended-release vaginal rings with release rates of 4.5 and 13.5ug/day administered for two consecutive menstrual cycles. The median for the menstrual cycle duration is 25.5-28.0 days while the bleeding duration median is 4.0-5.0 days. Transvaginal ultrasound to monitor follicular and corpus luteum development was performed in baseline cycle and after two treatment cycles. Neither of the two release rates affected the serum reproductive hormones. Corpus luteum development was identified in 93% of the women after two cycles. Serum follicle stimulating hormone, luteinizing hormone, estradiol, and progesterone levels were determined in the early follicular or mid-luteal phases. The endometrial histology at mid-luteal phase for both release rates is consistent with secretory endometrium. Table 4 summarizes the clinical studies on the efficacy and safety of DRD2-A in the treatment of endometriosis.

Effect on core outcomes in evaluating treatments for endometriosis-associated infertility

No studies evaluated the core outcomes recommended by Duffy et al.,[111] which included the primary outcome of live birth rate and several secondary outcomes including clinical pregnancy rate, multiple birth rate, ectopic pregnancy, miscarriage, stillbirth, time to pregnancy leading to live birth, gestational age at delivery, birthweight, neonatal mortality, major congenital abnormalities, recurrence rate of endometriosis, and patient satisfaction with treatment.

Safety of DRD2-A in endometriosis and infertility clinical studies

There were five studies[123-125,127,129] on the side effects and adverse events in the use of DRD2-A (cabergoline and quinagolide) in endometriosis. There were no reported serious adverse events and all were well-tolerated. However, there was one study[127] which showed that all five patients who received cabergoline complained of abnormal uterine bleeding.

DISCUSSION

This comprehensive review aimed to determine the efficacy and safety of DRD2-A for improving reproductive outcomes in women with endometriosis and infertility. Our searches did not find any studies that used the core outcomes[111] for trials evaluating potential treatments for infertility associated with endometriosis. Thus, the review focused on the determination of the effects of DRD2-A on angiogenesis, ovulation, and menstrual cyclicity. Studies on the safety profile of DRD2-A were also included.

Efficacy of DRD2-A on endometriosis: anti-angiogenesis

DRD2-A act in an autocrine fashion by binding to the DRD2 which subsequently trigger endocytosis of VEGFR-2, the critical step for promoting angiogenesis. So, the study on identification and quantification of both DRD2 and VEGFR2 in human eutopic and ectopic endometrium supported the theory that DRD2-A can be used for the treatment of endometriosis.[120] Despite that there was no statistical differences in DRD2 and KDR expression between the groups treated with low and high doses of cabergoline and controls, there was a trend toward an increased expression of DRD2 and lower expression of KDR when cabergoline doses were given. On top of it, VEGF expression was significantly decreased in lesions treated with the low and high doses of cabergoline compared to controls. These findings suggested that DRD2-A may stimulate expression of DRD2 which will lead to more binding of DRD2-A and result to reduced angiogenesis and increased regression/atrophy of endometriotic lesions.

Based on the results of the review, the use of DRD2-A led to reduction of endometrial lesions except in two studies: 1) the pioneer study of Novella-Maestre et al.,[68] which did not decrease lesion size, but, demonstrated a significant reduction in the number of glands and lax stroma with lost cellularity and organization which are characteristic of atrophic or degenerative tissues and 2) the recent pre-clinical study[116] where a number of rats died during the experiment which might have cause the loss of significant data.

Although, initial pre-clinical studies[58,112,119] showed no significant difference in microvessel density, the latest study by Tejada et al.,[118] subsequently proved significantly lower microvessel density after adjusting the timing of administration a few days after graft implantation when vessels are more sensitive to antiangiogenic stimuli. Moreover, that same study used an antiangiogenic reference group, CBO-P1, to standardize the range of the effects of the treatments which showed that the extent of the anti-angiogenic effects were similar in both groups. For the clinical study, the proof of

concept study by Gomez et al.,[123] detected no difference in vascular density and quantity of immature vessels which was conflicting with the 69.5% reduction in the size of the lesions, with 35% of the lesions vanishing completely. Questions on the results included whether the anti-angiogenic effect was masked or was it caused by another mechanism.

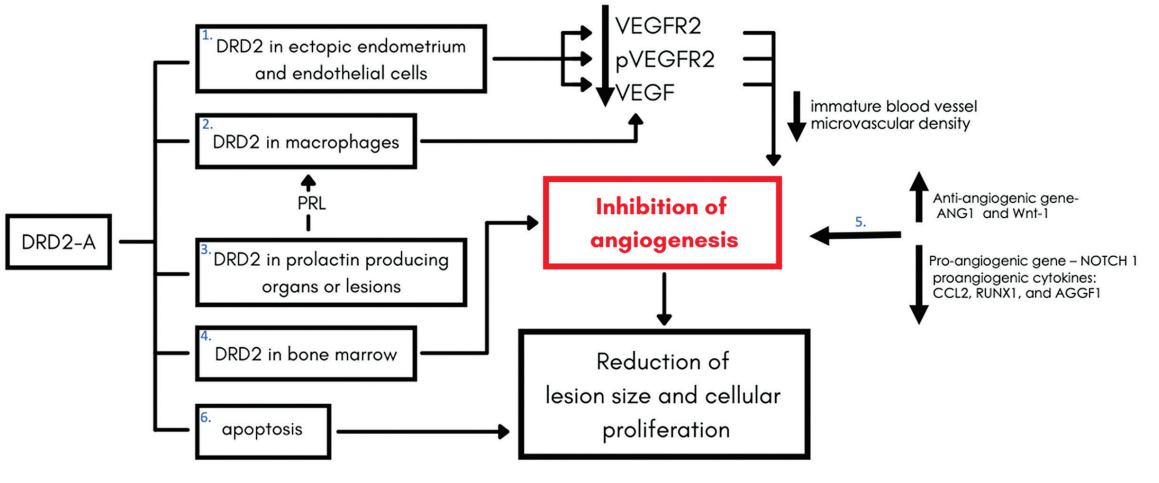
Most studies, both pre-clinical and clinical studies, at the molecular level showed significant reduction in VEGF protein expression, VEGFR2 protein expression, and phosphorylation resulting to the observed inhibition of neoangiogenesis. The genetic study on the use of quinagolide showed lower expression of VEGF mRNA levels which was postulated to be an alternative mechanism for the anti-angiogenic effect of DRD2-A. So, aside from the classical autocrine fashion, dopamine agonists can act in a paracrine fashion where they will bind to DRD2 in macrophages. This binding will result to reduced expression of *VEGF-A* mRNA levels and thus reducing the VEGF-A levels within the lesions.[112]

Thus, the summary of all the results of this review supports the possible anti-angiogenic effects of DRD2-A on the VEGF/VEGFR system. This is in agreement with the results of the recent review on experimental and clinical data on the use of DRD2-A to target angiogenesis in women with endometriosis.[72]

Aside from the VEGF/VEGFR pathway, there are also other parallel mechanisms which can contribute to the findings in this review. Endometriotic lesions have been found to be associated with hyperprolactinemia,[129-137] but whether the elevated prolactin stimulated the growth of the endometriosis or the endometriotic lesions are producing the hormone is still controversial. The associated hyperprolactinemia has been suggested to be a possible cause of the ovulatory dysfunction and infertility[133–138] to these patients with minimal-mild endometriosis without tubal occlusion.[134] Prolactin possesses an angiogenic effect and prolactin-treated macrophages showed an enhanced release of VEGF.[139] With the DRD2-A inhibiting prolactin secretion, there will be less VEGF production from the macrophages, less vascularization, thus, reducing the endometriotic lesions. Another plausible mechanism is the binding of DRD2-A to their receptors inhibited mobilization of endothelial progenitor cells [EPC] from the bone marrow preventing their subsequent contribution in neoangiogenesis.[140] Lastly, the findings of significant elevation in the number of apoptotic cells in the treated groups[118] may have contributed to the regression of endometriotic lesions. (Figure 4)

Most of the pre-clinical and clinical studies reviewed demonstrated that DA were effective in reducing endometriotic lesions (Figure 5). However, further research is required to establish whether this anti-angiogenic effect can improve reproductive outcomes in women with endometriosis-associated infertility. In addition, future studies should use the core outcomes[111] to evaluate the potential of DRD2-A as infertility treatment.

New studies that will define the patient profile who will most benefit from anti-angiogenic therapy are needed. Since DRD2-A seemed to target new lesions with immature vessels, studies on their use to prevent new lesions after surgery or to prevent recurrence maybe investigated. Moreover, studies on combining them with other medical treatment that



(1) DRD2-A increases DRD2 in in ectopic endometrium and endothelial cells. Subsequent binding of DRD2-A to its receptor will decrease VEGF, VEGFR2 and pVEGFR2 in autocrine fashion resulting to reduced immature blood vessels and lower vascular density. (2) The binding of DRD2-A in the DRD2 in macrophages decreases VEGF levels in a paracrine fashion. (3) The associated hyperprolactinemia in endometriosis will be lowered by DRD2-A. The reduction of prolactin will inhibit macrophage to stimulate VEGF release. (4) DRD2 inhibit mobilization of endothelial progenitor cells (EPCs) from the bone marrow. All these will lead to inhibition of angiogenesis. Loss of vascularization to the endometriotic lesions will lead to reduction of the size and cellular proliferation. (5) The upregulation of anti-angiogenic genes ANG1 and Wnt-1 and downregulation of the pro-angiogenic gene NOTCH1 and proangiogenic cytokines (CCL2, RUNX1 and AGGF1) will further reduce angiogenesis. (6) Apoptosis will contribute to further regression of the endometriosis

Figure 4. Suggested mechanisms of action of dopamine agonists on endometriosis.

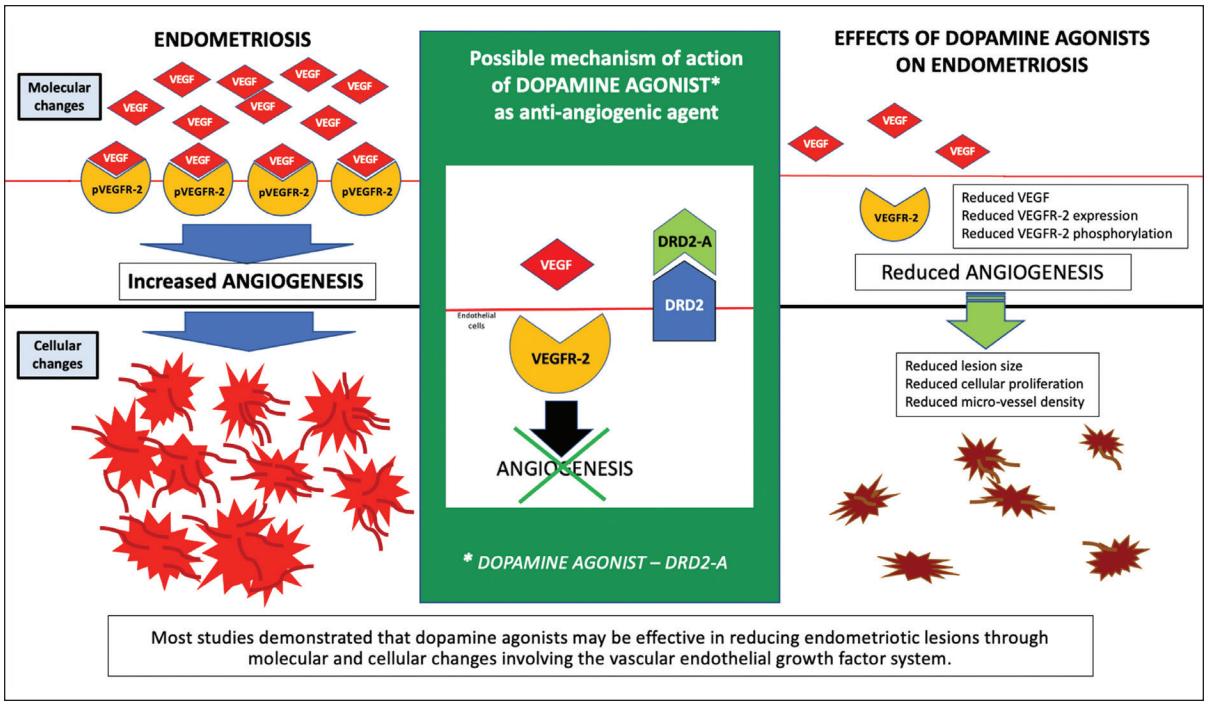


Figure 5. Graphical abstract showing the possible effects of dopamine agonists in endometriotic lesions.

will address later stages of endometriosis or rectovaginal endometriosis which have a higher percentage of mature vessels should be explored. Aside from safety, studies on tolerability can also be investigated to ensure patient's compliance. Lastly, the future studies recommended above must be appropriately-designed, adequately powered, randomized and controlled clinical trials of the highest quality to determine the efficacy and safety of DRD2-A for endometriosis-associated infertility to avoid bias in the conduct of the research.

Efficacy of DRD2-A on ovulation, menstrual cyclicity, reproductive hormones and endometrial histology

Unlike with the traditional hypoestrogenic treatment for endometriosis, the use of DRD2-A does not have an effect on ovulation, menstrual cyclicity, reproductive hormones, and endometrial histology[128] thus maintaining the normal hypothalamic-pituitary ovarian axis and ovarian function which are very important for women who are desirous of getting pregnant. However, more clinical trials will be needed to assess if the above findings will translate to better fertility outcomes for women with endometriosis-associated infertility.

Safety profile of DRD2-A for endometriosis

The results of the review on the safety profile of DRD2-A - bromocriptine, cabergoline and quinagolide- are similar with existing data.[72] Since 5-18% of patients had bromocriptine resistance[141] and the ergot-derived cabergoline was associated with increased incidence of cardiac valve regurgitation with long-term use,[142] Quinagolide seems to be the better alternative. The lower side effect profile, simple and rapid titration over just seven days and the once-daily dosing regimen may improve patient compliance.[141] Moreover, it is not teratogenic nor embryotoxic[141] and did not show adverse effects on implantation, pregnancy or live birth rate.[80]

As a drug class, DRD2-A are associated with gastro-intestinal side effects including nausea and vomiting. Thus, the vaginal route of administration will be a better option so there will be less gastrointestinal side effects, better absorption, and no first pass effect.[143] In fact, in a clinical phase 1 study, Quinagolide vaginal rings were more bioavailable and were associated with lower incidence of adverse events compared to the oral tablet.[128]

Limitation of findings

The significant anti-angiogenic effects of DRD2-A did not prove that the agents can improve the reproductive outcomes of those women with endometriosis-associated infertility. Furthermore, it should be noted that the development of new blood vessels in endometriotic lesions is mediated by various angiogenic factors and angiogenic signaling pathways and not only by the VEGF/VEGFR pathway.[28]

CONCLUSION

The review aimed to determine the efficacy and safety of DRD2-A for improving reproductive outcomes in women with endometriosis-associated infertility. Based on the limited data available, the results are not generalizable.

Most of the studies reviewed demonstrated that DRD2-A were effective in reducing endometriotic lesions.

Ethical Clearance

Exemption from ethical review was requested from and approved by the University of the Philippines Manila Research Ethics Board. The study did not involve collection, retention and processing of personal information.

Disclaimer

Views expressed in this article are from the author and not an official position of the institution.

Acknowledgments

The author would like to thank her husband, Bien and her three kids (Al, Ina and Franco) for being patient and understanding while she did this manuscript. The author is also very grateful to her mentors and colleagues from the College of Medicine, University of the Philippines Manila, including Dr. Raymond V. Oliva, Dr. Stephanie Fay S. Cagayan, Dr. Maria Antonia E. Habana, Dr. Enrico Gil C. Oblepias, and Mr. Essel N. Tolosa, and Dr. Elena Labarta Demur from the Valencian Institute of Infertility (IVI), for all their help and assistance.

Statement of Authorship

The author certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The author declared no conflicts of interest.

Funding Source

The funding was part of the Master's Fellowship Program of the Office of the Vice President for Academic Affairs of the University of the Philippines for the author's Master's Degree in Biotechnology in Human Assisted Reproduction and Embryology, Valencian Infertility Institute (IVI) Global Education, University of Valencia, Spain.

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APPENDIX

Outcomes identified for trials evaluating potential treatments for infertility associated with endometriosis (Duffy et al., 2020), known as the core outcome set

Primary outcome:

- Live birth rate – Delivery of a fetus after 22 completed weeks of gestational age (Grammatis et al., 2021).

Secondary outcomes:

- Clinical pregnancy – A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intra-uterine pregnancy, it includes a clinically documented ectopic pregnancy (Zegers-Hochschild et al., 2017).
- Multiple birth rate – Number of twin, triplet, or high-order pregnancies (specified if possible) per pregnancy and confirmed by ultrasound or delivery (Grammatis et al., 2021).
- Ectopic pregnancy – A pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualization or Histopathology, per couple/woman (Zegers-Hochschild et al., 2017).
- Miscarriage – Spontaneous loss of a clinical pregnancy before 22 completed weeks of gestational age, in which the embryo(s) or fetus(es) is/are nonviable and is/are not spontaneously absorbed or expelled from the uterus (Zegers-Hochschild et al., 2017).
- Stillbirth – The death of a fetus prior to the complete expulsion or extraction from its mother after 28 completed weeks of gestational age. The death is determined by the fact that, after such separation, the fetus does not breathe or show any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles. Note: It includes deaths occurring during labor (Zegers-Hochschild et al., 2017).
- Time to pregnancy leading to live birth – The time taken to establish a pregnancy, measured in months or in numbers of menstrual cycles. (Zegers-Hochschild et al., 2017).
- Gestational age at delivery – Extremely preterm is birth that takes place after 22 but before 28 completed weeks of gestational age. Preterm is a birth that takes place after 22 weeks and before 37 completed weeks of gestational age. Post-term A live birth or stillbirth that takes place after 42 completed weeks of gestational age. (Zegers-Hochschild et al., 2017).
- Birthweight – Low birth weight is birth weight less than 2500 g. Extremely low birth weight is birth weight less than 1000 g. (Zegers-Hochschild et al., 2017).
- Neonatal mortality – Death of a live born baby within 28 days of birth. This can be sub-divided into a) early, if death occurs in the first 7 days after birth; and b) late, if death occurs between 8 and 28 days after birth. (Zegers-Hochschild et al., 2017).
- Major congenital abnormalities – A congenital anomaly that requires surgical repair of a defect, is a visually evident or life-threatening structural or functional defect, or causes death (Zegers-Hochschild et al., 2017).
- Recurrence rate of endometriosis – surgically visualized, diagnosed by ultrasonography or recurrence of symptoms (Grammatis et al., 2021).
- Patient satisfaction with treatment