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Review Article

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ANGPT2 as a Therapeutic Target in Endometriosis: Evolving Perspectives in Angiogenesis - *ANGPT2*, an Emerging Target in Endometriosis Therapy

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ABSTRACT

Endometriosis is a chronic, estrogen-dependent inflammatory condition marked by the ectopic implantation of endometrial-like tissue, most commonly involving the ovaries, peritoneum, and pelvic structures. This ectopic tissue responds to hormonal cycles, leading to symptoms such as pelvic pain, dysmenorrhea, dyspareunia, and infertility. A critical process in the pathophysiology of endometriosis is angiogenesis, which sustains lesion growth and survival. Angiopoietin-2 (Ang-2), encoded by the *ANGPT2* gene, is a key regulator of abnormal vascular remodeling in endometriosis, acting as a vascular destabilizer and enhancing angiogenic responses, particularly in conjunction with vascular endothelial growth factor (VEGF).

This review synthesizes current evidence on the pathological role of Ang-2 in endometriosis-associated angiogenesis and evaluates its potential as a molecular target for therapy. A comprehensive literature search was performed using PubMed, Scopus, Google Scholar, and Web of Science, covering articles published from 1997 to 2025. Relevant studies were selected based on Ang-2's involvement in angiogenesis, its expression patterns in endometriotic tissue, and the outcomes of therapeutic interventions.

The findings reveal that *ANGPT2* expression is upregulated in endometriotic lesions and is modulated by hypoxia, estrogen, and inflammatory factors. Elevated levels of Ang-2 are associated with increased disease severity and vascular immaturity in lesions. Preclinical studies targeting Ang-2, either alone or in combination with VEGF inhibitors, have demonstrated reductions in lesion vascularization and growth, highlighting its therapeutic promise.

In conclusion, Ang-2 serves as a critical mediator of pathological angiogenesis in endometriosis and presents a promising target for novel anti-angiogenic therapies. Further translational research and clinical trials are warranted to explore its full therapeutic potential.

KEYWORDS angiogenesis, ectopic endometrial tissue, endometriosis, therapeutic targets, vascular endothelial growth factor, vascular remodeling

INTRODUCTION

Endometriosis is a chronic and debilitating disease characterized by the presence of endometrial tissue, including glandular epithelium and stroma, outside the uterine cavity (1-3). The World Health Organization (WHO) highlights its profound impact on quality of life, causing pelvic pain, fatigue, depression, infertility, dysmenorrhea, and even malignant transformations. It affects approximately 6.0% of women, with another 5.4% suspected of having the condition (4–6).

In endometriosis, retrograde menstruation introduces menstrual blood into the peritoneal cavity, leading to oxidative stress and immune responses. These changes promote the release of inflammatory cytokines and pro-angiogenic factors that disrupt the peritoneal microenvironment (7, 8). Angiogenesis, essential for endometrial growth and repair during the menstrual cycle, is similarly central to the pathophysiology of endometriosis (9, 10). It also plays a pivotal role in other gynecological disorders such as abnormal uterine bleeding and endometrial cancer (11–13).

Throughout the menstrual cycle, angiogenesis and vascular remodeling establish new vasculature in the endometrium, facilitating cell proliferation and differentiation (14). This process is tightly regulated by several angiogenic factors including vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), C-X-C motif chemokine ligand 12 (CXCL12), and IL-6, whose expression is modulated by hypoxia and sex hormones (15). VEGF, a potent signaling protein, promotes endothelial proliferation and neovascularization. In endometriosis, VEGF is upregulated in ectopic lesions, peritoneal fluid, and serum, supporting lesion establishment and progression via hypoxia, inflammation, and estrogen signaling.

Among the angiogenic mediators, Ang-2 has recently emerged as a key player in the angiogenesis pathway (16). Ang-2 interacts with VEGF in a regulatory network that governs endometrial angiogenesis (17, 18). While Ang-1 stabilizes blood vessels by enhancing endothelial junctions, Ang-2 competes for the same receptor to promote vascular remodeling and destabilization (19–23). Selectively expressed in the ovary, uterus, and placenta, Ang-2 facilitates VEGF-driven angiogenesis by weakening cell–cell and cell–matrix adhesion (24–26).

Elevated *ANGPT2* expression and enhanced angiogenic activity have been observed more frequently in women with endometriosis compared to unaffected individuals (10, 27). *ANGPT2* is thus considered a promising therapeutic target, with both *in-vitro* and *in-vivo* studies exploring its modulation via mRNA regulation and other strategies (28, 29). In this manuscript, *ANGPT1*, *ANGPT2*, *ANGPT3*, and *ANGPT4* are denoted as gene symbols, while Ang-1 and Ang-2 refer to their protein forms to reflect functional roles in angiogenesis. Despite emerging insights, the precise molecular mechanisms of *ANGPT2* remain to be fully elucidated. This study investigates factors influencing *ANGPT2* expression, its therapeutic potential in endometriosis, and the clinical value of targeting Ang-2 in anti-angiogenic therapy.

METHOD

A comprehensive literature review was conducted to explore the role of *ANGPT2* in the pathogenesis and therapeutic potential in endometriosis. Biomedical databases, including PubMed, Scopus, Web of Science, and Google Scholar, were searched using relevant keywords such as angiogenesis, ectopic endometrial tissue, endometriosis, therapeutic targets, VEGF, and vascular remodeling. Boolean operators were applied to refine search results, and filters such as clinical trials, systematic reviews, publication within the last five years, and free full-text availability, were used to enhance relevance. From an initial yield of nearly 20,000 articles, screening based on titles, abstracts, and full-text review narrowed the selection to 74 key publications that offered substantial insights into *ANGPT2*'s involvement in vascular remodeling, inflammation, hormonal regulation, and angiogenic imbalance in endometriosis. Both preclinical and clinical studies were included to provide a comprehensive understanding of the molecular and translational aspects of *ANGPT2* in disease progression and its potential as a therapeutic target.

Physiological angiogenesis in the endometrium

The human endometrium undergoes cyclic growth and regeneration in response to hypoxia and sex steroid interactions throughout the menstrual cycle (12, 30). These dynamic changes are closely associated with angiogenesis, a tightly regulated process by which new blood vessels

form through sprouting, elongation, and intussusception by endothelial cells (11, 12). Angiogenesis plays a fundamental role in endometrial remodeling necessary for reproduction, including follicular maturation, corpus luteum function, and uterine preparation for implantation.

Endometrial vascular development is finely controlled by the interaction of pro-angiogenic and anti-angiogenic factors, ensuring appropriate vessel formation and remodeling. Hypoxia and female sex hormones independently influence the expression of these factors, thereby maintaining vascular homeostasis under both physiological and pathological conditions, including the progression of endometriosis (15, 31). Pro-angiogenic signals stimulate endothelial activation and vessel sprouting, while anti-angiogenic molecules constrain excessive neovascularization, maintaining vascular stability (15, 32).

Key pro-angiogenic mediators involved in this regulatory network include VEGF, angiopoietins, chemokine CXCL12, fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), and matrix metalloproteinases (MMPs). These promote vascular growth and endothelial cell activity. Conversely, anti-angiogenic molecules such as soluble VEGF receptor-1 (sVEGFR-1), endostatin, maspin, and thrombospondin-1 (TSP-1) act as inhibitory controls. This intricate balance governs not only cyclic endometrial regeneration but also broader physiological processes like wound healing, and plays a role in pathological conditions such as cancer and endometriosis. Understanding the modulation of these pathways offers potential for targeted angiogenic therapies.

This coordinated regulation of angiogenic balance is illustrated in Figure 1, where pro-angiogenic molecules (e.g., VEGF, *ANGPT*, epidermal growth factor (EGF), PDGF), denoted by upward arrows, enhance endothelial activation and vessel formation, while anti-angiogenic factors (e.g., sVEGFR-1, endostatin, maspin, TSP-1), indicated by downward arrows, serve to inhibit the process. The figure underscores the dynamic interplay of these opposing factors in governing angiogenesis.

Role of *ANGPT1 and ANGPT2* in endometrial vascular remodeling

Angiopoietins play a crucial role in regulating blood vessel growth, maturation, and regression, working in close coordination with VEGF to modulate angiogenesis (23, 33, 17). The angiopoietin family includes *ANGPT1*, *ANGPT2*, *ANGPT3*, and *ANGPT4*, of which *ANGPT1* and *ANGPT2* are the most extensively studied (34, 35). While *ANGPT1* is widely expressed across various tissues, *ANGPT2* expression is predominantly localized to the ovary, uterus, and placenta. In the human endometrium, their expression patterns vary with the menstrual cycle. During the secretory phase, Ang-1 is primarily localized around blood vessels in the stromal region, whereas Ang-2 is expressed in the glandular epithelium and endothelium (24, 36).

Functionally, Ang-1 binds to the Tie-2 receptor to promote blood vessel stability, integrity, and quiescence. It also supports physiological angiogenesis during ovulation by maintaining endothelial cell survival and vessel maturation. In contrast, Ang-2 acts as a natural antagonist of Ang-1 by competitively binding to Tie-2 without activating it, thereby inhibiting Tie-2 signaling (37, 38). This results in vessel destabilization and extracellular matrix loosening—key preparatory steps for angiogenesis.

The action of Ang-2 is highly context-dependent. In the presence of VEGF, Ang-2 facilitates endothelial proliferation and sprouting, promoting

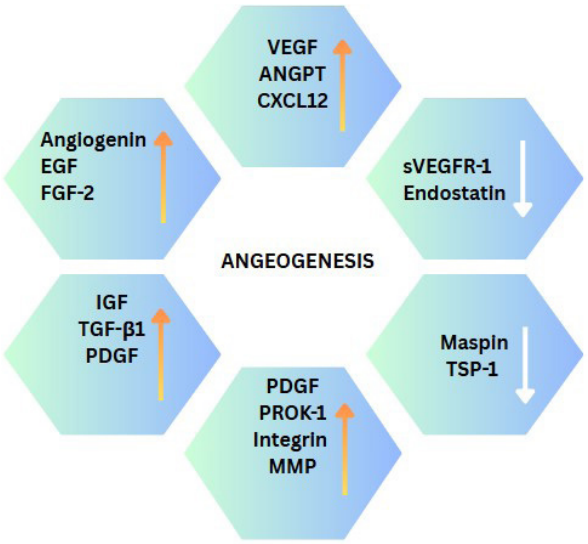

Figure 1. An illustration of the complex network of pro-angiogenic and anti-angiogenic factors involved in angiogenesis, highlighting key molecular mediators such as VEGF, *ANGPT*, CXCL12, and TSP-1, and their regulatory roles in vascular development and remodeling. Orange upward arrows indicate pro-angiogenic factors, while white downward arrows represent anti-angiogenic factors.

neovascularization. However, in the absence of VEGF, Ang-2-induced destabilization leads instead to vessel regression due to impaired pericyte recruitment and endothelial disassembly (23, 25, 26). This dual functionality makes Ang-2 a pivotal modulator of vascular plasticity, capable of either promoting or inhibiting angiogenesis depending on the angiogenic milieu.

The dynamic balance between Ang-1 and Ang-2 is essential for endometrial vascular remodeling, especially during cyclic regeneration and implantation. An increased Ang-2/Ang-1 ratio is indicative of vascular destabilization—a prerequisite for new vessel formation—and may serve as a marker of endothelial activation and remodeling capacity (39). This tightly regulated angiopoietin-Tie2 signaling axis ensures proper vascular adaptation throughout the menstrual cycle and reproductive processes.

Molecular regulation of *ANGPT2* expression

Hypoxia serves as a central regulator of endometrial angiogenesis during the premenstrual period. As oxygen levels decline during menstruation, hypoxia-inducible factor-1α (*HIF-1α*) stabilizes and activates key proangiogenic genes such as *VEGF*, *ANGPT1*, *ANGPT2*, Tie-2, PDGF, basic fibroblast growth factor (*bFGF*), and monocyte chemoattractant protein-1 (*MCP-1*), thereby initiating vascular remodeling processes (40–42). Under hypoxic conditions, *ANGPT1* expression markedly decreases, while *ANGPT2* levels remain relatively stable, leading to an elevated *ANGPT2/ANGPT1* ratio. This imbalance, especially in the presence of VEGF, promotes endothelial destabilization and subsequent neovascularization (43). Additionally, hypoxia induces the expression of other angiogenic mediators like CYR61 and leptin, and upregulates osteopontin and cysteine-rich protein 61 via the COX-2/prostaglandin pathway. Estrogen and prostaglandins also enhance *HIF-1α* stabilization, establishing a positive feedback loop that intensifies the hypoxia-driven angiogenic cascade. This loop modulates both angiogenic and anti-angiogenic factors, thereby fine-tuning *ANGPT2* activity and vascular dynamics in the endometrium (44).

Importantly, the influence of hypoxia on angiopoietin expression extends to extra-endometrial sites. In the hypoxic peritoneal microenvironment characteristic of endometriosis *HIF-1α* suppresses the transcription factor chicken ovalbumin upstream promoter-transcription factor II, resulting in increased angiopoietin levels and enhanced vascularization of ectopic lesions (45).

Female steroid hormones, notably estrogen and progesterone, also exert critical control over *ANGPT2* expression. Estrogen upregulates VEGF and downregulates *ANGPT1*, thereby increasing the *ANGPT2/ANGPT1* ratio and fostering a pro-angiogenic environment favorable for endometrial vessel development (46). In contrast, progesterone displays a nuanced role. During the secretory phase, it supports vascular maturation. Progestins reduce *ANGPT2* while maintaining *ANGPT1*, effectively lowering the *ANGPT2/ANGPT1* ratio and exerting anti-angiogenic effects (43). In early pregnancy, *ANGPT2* expression in the uterine endometrium is modulated by progesterone, likely contributing to vascular remodeling via the Tie-2 pathway. Supporting this, progesterone has been shown to upregulate *ANGPT2* in human uterine microvascular endothelial cells (HUtMECs), underlining its role in gestational angiogenesis (47).

In hypoxic, inflammatory conditions like endometriosis, elevated *ANGPT2* levels activate the Ang-2/Tie2 signaling axis, which antagonizes *ANGPT1*-mediated vessel stabilization. This shift facilitates VEGF-A-driven endothelial proliferation and migration, promoting pathological angiogenesis (48). Pichiule et al. demonstrated that hypoxia enhances *ANGPT2* expression in endothelial cells through both transcriptional mechanisms and mRNA stabilization, resulting in increased intracellular and secreted Ang-2 protein levels.

Estrogen further promotes endometrial angiogenesis by stimulating endothelial cell proliferation, migration, and vessel stabilization (49). However, in endometriosis, heightened estrogenic activity intensifies inflammation, pain, and infertility by upregulating VEGF and suppressing *ANGPT1*, thus raising the *ANGPT2/ANGPT1* ratio and driving aberrant vascular growth (46, 50). Although progesterone ordinarily regulates inflammation and decidualization, impaired signaling in endometriosis contributes to ectopic tissue implantation and disease progression (51). Typically, post-ovulatory progesterone surge limits endometrial proliferation (52), but in endometriosis, progesterone resistance exacerbates the

ANGPT2/ANGPT1 imbalance, further promoting pathological angiogenesis (43, 53).

ANGPT2 in endometriosis pathogenesis

In endometriosis, retrograde menstruation allows menstrual blood to enter the peritoneal cavity, triggering oxidative stress and immune responses. This disrupts peritoneal homeostasis and promotes the release of pro-angiogenic factors that drive neovascularization and the formation of microvascular networks (7, 8). Pathological angiogenesis, characterized by unregulated blood vessel growth, results from dysregulation in key signaling pathways Fsuch as VEGF, Notch, Angiopoietin-Tie, and FGF (15). The eutopic endometrium of affected individuals exhibits elevated angiogenic potential, with increased expression of Ang-1 and Ang-2 compared to non-endometriotic tissue. As angiogenesis is essential for the establishment and maintenance of endometriotic lesions, targeting Ang-2 has emerged as a promising therapeutic approach (27, 54, 29).

Neovascularization is central to endometriosis progression, with Ang-2 functioning as a critical modulator (55, 26). Overexpression of *ANGPT2* in both ectopic and eutopic endometrial tissues contributes to lesion development and is being explored as a potential biomarker for disease severity. In synergy with VEGF, Ang-2 enhances the production of MMPs, particularly MMP-1 and MMP-9, which facilitate tissue invasion and remodeling. Moreover, Ang-2 promotes vessel sprouting by antagonizing the stabilizing effect of Ang-1 on the Tie2 receptor (55, 27), a mechanism further supported by studies demonstrating functional interplay between Ang-2 and VEGF (29). The Ang-2/Ang-1 ratio increases during early angiogenic phases and fluctuates with disease progression, reflecting dynamic vascular demands (56). Dysregulated ANGPT signaling has also been associated with reproductive complications, including miscarriage (57).

Clinical studies have shown significantly elevated levels of VEGF, Ang-1, Ang-2, MMP-1, and MMP-9 in the eutopic endometrium of endometriosis patients compared to controls, reinforcing their role in disease pathophysiology (58). Sampson's seminal theory of retrograde menstruation, proposed in 1925, remains the most widely accepted explanation for endometriosis development (59–61). An endometrial environment enriched with angiogenic and proteolytic factors is more likely to give rise to ectopic implants upon migration into the peritoneal cavity (58). Notably, Hur et al. reported that during the secretory phase, the *ANGPT2/ANGPT1* mRNA expression ratio was significantly elevated in eutopic endometrium from women with endometriosis relative to healthy controls. The predominance of Ang-2 over Ang-1 at the Tie2 receptor, in the presence of VEGF, may lead to persistent immature neovascularization—a hallmark of endometriotic lesions (27).

Therapeutic targeting of *ANGPT2* in endometriosis

Zhou et al. identified miR-205-5p as a pivotal regulatory molecule in endometriosis, demonstrating its role in controlling ectopic endometrial stromal cell migration, invasion, and apoptosis by directly targeting *ANGPT2* and modulating the Ang-2–AKT/ERK signaling pathway. Their findings revealed an inverse relationship between miR-205-5p and *ANGPT2* expression, with reduced miR-205-5p and elevated *ANGPT2* levels correlating with greater disease severity, thereby positioning the miR-205-5p–*ANGPT2* axis as a promising and highly specific therapeutic target. Unlike broad-spectrum anti-angiogenic therapies that may compromise normal vascular integrity and lead to systemic adverse effects, *ANGPT2*-targeted interventions selectively disrupt pathological neovascularization within endometriotic lesions, preserving healthy vasculature. Additionally, miRNA-based or *ANGPT2*-specific approaches allow for localized delivery, reducing systemic exposure and enhancing treatment safety (28).

Similarly, Chen et al. demonstrated that administration of the traditional Chinese medicine Hua Yu Xiao Zheng (HYXZ) decoction in a rat model of endometriosis significantly reduced lesion size and downregulated VEGF and *ANGPT2* expression. While VEGF inhibition remains a conventional anti-angiogenic strategy, *ANGPT2* targeting offers a more refined approach by destabilizing vasculature specific to ectopic endometrial tissue. This focused inhibition may improve disease control while minimizing vascular-related side effects, reinforcing *ANGPT2*'s dual role as a biomarker and therapeutic target (29).

Endometriosis-associated angiogenesis provides a strong rationale for anti-angiogenic therapy as a targeted, non-hormonal treatment option. To this end, various angiogenic blockers have been evaluated, offering alternatives to hormone-based therapies (32). Table 1 summarizes various pharmacological agents with anti-angiogenic effects on endometriosis.

Angiogenesis is central to ectopic lesion establishment and progression. Its dysregulation, particularly the overexpression of *ANGPT1* and *ANGPT2* in eutopic endometrial tissues, contributes significantly to the disease pathophysiology (27, 68). In the presence of *VEGF*, *ANGPT2* promotes MMP activation, facilitating tissue invasion (69). Its dominance over *ANGPT1* via the Tie-2 receptor further promotes immature and persistent neovascularization (70, 71). Thus, inhibiting *ANGPT2* may effectively curb aberrant angiogenesis, suppress lesion growth, and improve overall disease outcomes (28).

Unlike conventional anti-angiogenic treatments that broadly suppress vascular proliferation, *ANGPT2*-specific therapies offer greater precision by selectively targeting abnormal and immature vessels within endometriotic lesions. This mechanism helps to minimize off-target effects and preserve normal vascular function. Moreover, these therapies are amenable to localized delivery methods, such as intra-peritoneal administration or direct lesion injection, further reducing systemic toxicity.

In contrast to hormone-based treatments often associated with undesirable effects including androgenic symptoms (e.g., increased facial hair, deepened voice), weight gain, fluid retention, acne, mood instability, and heightened risk of thromboembolism, *ANGPT2*-targeted therapies offer a more favorable safety profile (72).

Clinically, *ANGPT2* inhibition has demonstrated multiple benefits: more precise lesion suppression, reduced pelvic pain, fewer ectopic implants, lower microvascular density, enhanced apoptosis, decreased VEGF levels in peritoneal fluid, fibrosis of endometriotic lesions, resolution of refractory dysmenorrhea, and upregulation of hormone receptor expression in affected tissues (32, 63, 73, 74). These outcomes underscore the potential of *ANGPT2* as both a therapeutic target and as a prognostic indicator in the effective management of endometriosis.

Safety considerations and limitation of *ANGPT2*-targeted therapies

Anti-angiogenic therapy may adversely impact normal physiological processes such as ovulation and wound healing. As a result, it may have adverse impacts on reproductive function and pose teratogenic risks when used to treat endometriosis in women of reproductive age (32). The therapeutic approach towards regulating Ang-2 for endometriosis requires further investigation to fully understand its benefits and potential consequences. More studies are needed to comprehensively

Table 1. Summary of various pharmacological agents with anti-angiogenic effects on endometriosis, detailing their mechanisms of action such as VEGF inhibition, *HIF-1α* suppression, and MMP regulation, which contribute to the reduction of lesion size and vascularization

Drug	Anti-angiogenic effects on endometriosis	Mode of action	Reference
Angiostatin	Restricts the number of endometriotic lesions	Inhibits VEGF and bFGF signaling	(62)
Anti-*VEGF* antibody	Reduces *VEGF* levels in peritoneal fluid and micro vessel density	Neutralizes active *VEGF* and blocks its receptor	(63)
2-Methoxyestradiol	Suppresses *HIF-1α* and *VEGF* expression	Inhibits *HIF-1α* expression and its transcriptional activity	(64)
Simvastatin	Reduces micro vessel density	Downregulates *VEGF* synthesis and suppresses MMP secretion	(65)
Celecoxib	Reduces micro vessel density	Inhibits COX-2	(66)
Retinoic acid	Reduces the volume of endometriotic implants	Directly downregulates *VEGF* production	(67)

VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor, HIF-α, hypoxia-inducible factor alpha

evaluate the effectiveness and safety of targeting Ang-2 in the management of endometriosis.

CONCLUSIONS

This study underscores the pivotal role of *ANGPT2* in endometriosis, with a particular focus on the regulatory mechanisms governing its expression and its therapeutic potential. The findings suggest that targeting Ang-2 may help alleviate endometriosis symptoms and enhance clinical outcomes by modulating key angiogenic signaling pathways.

However, several limitations must be considered. Much of the current evidence is derived from *in-vitro* or animal studies, which may not accurately reflect human physiological conditions. Moreover, the precise molecular mechanisms by which Ang-2 contributes to angiogenesis remain incompletely understood. Its regulation by hormones such as progesterone appears inconsistent, particularly in the context of progesterone resistance, a common feature in endometriosis.

While anti-angiogenic therapies targeting Ang-2 show therapeutic promise, they may also disrupt normal reproductive functions, including ovulation and wound healing, raising important safety concerns for women of reproductive age. Additionally, the lack of clinical trials validating Ang-2 as a therapeutic target highlights a critical gap, and it is likely that targeting Ang-2 alone may be insufficient due to the complex and redundant nature of angiogenic signaling networks in endometriosis.

Despite these challenges, this study offers a novel perspective by integrating the upstream regulatory influences of hypoxia, estrogen, and inflammatory mediators on *ANGPT2* expression within the endometriotic microenvironment. Unlike earlier studies that mainly reported elevated Ang-2 levels, our review emphasizes the dynamic regulation of Ang-2 and positions it not only as a biomarker of disease severity, but also as a dual-action therapeutic target capable of disrupting both pathological neovascularization and chronic inflammation.

This dual role enhances the rationale for developing Ang-2–focused therapeutic interventions as part of clinical management strategies for endometriosis. To fully realize this potential, further research is essential to validate these findings, clarify Ang-2's molecular functions, and rigorously assess the efficacy and safety of targeted anti-angiogenic therapies. Continued investigation will not only support therapeutic development for endometriosis but may also inform strategies for other gynecological disorders marked by aberrant angiogenesis.

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CONFLICT OF INTEREST

There was no conflict of interest in this manuscript.

AUTHOR CONTRIBUTION

S.M.J.: conceptualization of the study, methodology design, sample collection, laboratory work (biochemical and molecular analyses), data acquisition, statistical analysis, and manuscript drafting, support in genetic data analysis and visualization, referencing, and manuscript formatting; S.K.B.: supervision, critical review of study design, interpretation of molecular data, guidance in laboratory methodologies, and manuscript revision for important intellectual content; N.M.: validation of biochemical assay procedures, clinical correlation of metabolic findings, and critical inputs in manuscript development; K.R.K.: clinical insight into endocrine aspects, interpretation of hormonal and metabolic data, and contribution to discussion and conclusions; J.P.J., J.J., S.M., J.A.M.: assistance in sample processing, ELISA/RT-PCR experimentation, data entry, and preliminary statistical valuation; P.S., J.V.C., S.K.,: Support in genetic data analysis and visualization, referencing, and manuscript formatting; D.R.D.: conceptual supervision, molecular diagnostics consultation (MC4R expression), manuscript review, critical editing, and final approval of the version to be published.

DATA AVAILABILITY STATEMENT

This review is based on previously published studies. All data supporting the findings are available in the cited literature. Additional information can be provided by the authors upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

This review article does not report on new experimental research involving humans or animals; therefore, ethics approval was not required.

INFORMED CONSENT STATEMENT

This review article does not include research involving human participants; therefore, informed consent was not required.

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