NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

BARTKIEWICZ, Karolina, PAPIEŻ, Magdalena, JĘDRA, Zofia, LIBERA, Anna, KOZICKI, Maciej Jakub, KOSTRO, Julia Maria, NOVIK, Lizaveta, MAKULEC, Gabriela, DOMOSUD, Karolina, and ZIENKIEWICZ, Damian. Metformin as a New Therapeutic Option for Endometriosis: Promise, Limits, and Future Directions. Quality in Sport. 2026;54:70561. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70561

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 02.04.2026. Revised: 15.04.2026. Accepted: 22.04.2026. Published: 25.04.2026.

Metformin as a New Therapeutic Option for Endometriosis: Promise, Limits and Future Directions

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ABSTRACT

Endometriosis is a chronic, estrogen-dependent, inflammatory disease affecting a plethora of women of reproductive age and is a major cause of pelvis pain and subfertility. Current treatments – surgery and hormonal suppression are often only partly effective, lead to further fertility issues or have substantial adverse effects, creating an unmet need for a non-hormonal, disease modifying therapy option (Carvalho, J. C., et al; 2021). Metformin, a biguanide used worldwide as a first-line insulin-sensitizing drug for type 2 diabetes, has emerged as a therapeutic option for endometriosis because of its pleiotropic anti-inflammatory, anti-proliferative, anti-angiogenic and metabolic effects. This paper analyses mechanistic, preclinical and early clinical evidence on metformin use in endometriosis, with particular attention to how the drug interacts with the known pathophysiology of the disease (Kimber-Trojnar, Ż., et al; 2022). Rather than an immediate replacement for standard hormonal therapies, metformin currently appears best positioned as a promising adjuvant or alternative for selected patients – particularly those with co-existing metabolic dysfunction pending high-quality clinical trials (Zhang, H., et al; 2023).

Keywords: metformin, endometriosis

Introduction

Endometriosis is among the most enigmatic of gynecologic diseases. Although the literature is extensive the underlying cause as well as the best therapeutic options are still lacking.

Endometriosis is a chronic inflammatory disease defined by the presence of endometrium-like tissue outside the uterine cavity. Historically, the disease was described as two variants: endometriosis interna, now generally referred to as adenomyosis and endometriosis externa referring to ectopic endometrial glands and stroma outside the uterus. Some experts specify that the tissue has to be hormonally active to speak about the disease actually occurring (Jubanyik K.J. & Comite F.; 1997). Nowadays, in reported cases endometriosis usually denotes the extrauterine form most commonly involving the ovaries and pelvic peritoneum. Although atypical lesions may also occur in the gastrointestinal tract, urinary tract, soft tissues and the chest.

This broader anatomic range matters because the symptoms burden depends in part on lesion location. Pelvic disease is usually associated with dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia and infertility. Whereas extrapelvic disease may present with hematuria, bowel obstructions, cyclical chest symptoms or localized soft-tissue swelling (Sushikumar K. Sonavane, et al.; 2011).

Even so, the unifying pathobiology is not simply ectopic location. Endometriosis is now understood as more than a localized pelvic disorder; it involves systemic immune, inflammatory, hormonal and metabolic disturbances that help explain its chronicity and variable clinical presentation (Kimber-Trojnar, Ż., et al; 2022). The disease imposes a massive psychosocial and economic burden as well. Women frequently experience many years of diagnostic delays with repeated consultations in primary care, emergency departments and infertility clinics resulting in a prolonged interval between symptom onset and definitive diagnosis (Zondervan, K. T., et al.; 2018). This delay is associated with disease progression, entrenched pain pathways and substantial psychological distress including anxiety and depressive symptoms (Facchin, F., et al.; 2015). From a health economics perspective endometriosis also generates direct costs through surgeries, medications, absenteeism and reduced work capacity (Simoens S., et al.; 2012).

Standard treatment paradigms focus on two main strategies: surgical excision or ablation of visible lesions and suppression of ovarian function using combined oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists or antagonists and other hormonal agents (Dunselman G. A. J., et al.; 2014; Becker C. M., et al.; 2022). While these

therapies are effective for many patients, they present significant limitations as they are suppressive and not curative. Surgical approaches are associated with recurrence and operate at the threshold between radical removal and preservation of ovarian reserve (Vercellini P., et al.; 2014). Hormonal suppression, meanwhile is essentially contraceptive and can provoke hypoestrogenic side effects, impacting bone health, mood and sexual function (Dunselman G. A. J., et al.; 2014). It is also important to mention that many patients have entered the progesterone-resistant state. Therefore as a consequence hormonal therapy is rendered ineffective for a subset of women with endometriosis.

For these reasons, finding alternative treatment to propose as mono-therapy or in addition to already existing therapies should be a priority. As the understanding of endometriosis has evolved, so has the interest in non-hormonal, disease modifying therapies (Zondervan, K. T., et al.; 2018). One emerging candidate is metformin, a widely used insulin-sensitizing agent with well-described safety in long-term use (Rena G., et al.; 2017). Metformin acts through several pathways relevant to endometriosis pathophysiology: it activates AMP-activated protein kinase (AMPK), inhibits the mechanistic target of rapamycin (mTOR), modulates autophagy, reduces oxidative stress and exerts anti-inflammatory and anti-angiogenic effects (Kimber-Trojnar, Ż., et al; 2022). Due to the underlying issues in Endometriosis involving intersecting axes of estrogen dysfunction, chronic inflammation, angiogenesis and metabolic dysfunction, metformin offers an opportunity to target multiple disease mechanisms with a single oral drug (Burney, R.O. Giudice, L.C.; 2012; Kimber-Trojnar, Ż., et al; 2022).

The role of this paper is to evaluate the evidence supporting metformin as a potential treatment for endometriosis in a scientific and methods-oriented way. Not only whether metformin use is biologically plausible, but whether the design of the relevant studies supports a credible therapeutic role in endometriosis.

Pathophysiology of Endometriosis and the Rationale for Metabolic Theory

Multiple non-exclusive theories exist for the origin of endometriosis. The classic point of departure is Sampsons theory of retrograde menstruation. In this model menstrual effluent containing viable endometrial cells refluxes through the fallopian tubes into the peritoneal cavity, where implantation may occur (Giudice, L. C.: et al; 2010). This theory remains fundamental because it offers a direct route by which endometrial tissue reaches different ectopic sites. However, since retrograde flow is common in women who never develop endometriosis therefore the backflow alone cannot explain the disease. The key problem seems to be not just backflow, but the failure of immune clearance and to inactivate refluxed

endometrial fragments allowing them to adhere to peritoneal surfaces, survive and invade deeper tissues (Burney, R. O. et al 2009).

A second important framework treats ectopic lesions as autonomous steroidogenic units. Endometriotic implants overexpress aromatase and other steroidogenic enzymes, producing estradiol locally while also expressing COX-2 and prostaglandin E2 which further stimulate aromatase in a positive feedback loop (Bulun, S. E. et al., 2012). At the same time lesions and sometimes eutopic endometrium show progesterone resistance with altered progesterone receptor signaling and impaired anti-proliferative response (Vercellini, P. et al.; 2014). This endocrine profile helps explain persistent lesion activity and provides a rationale for therapies that interrupt growth signaling even without directly suppressing ovarian function.

A third theory emphasizes immune dysregulation. Women with endometriosis show altered innate and adaptive immunity. Peritoneal fluid in patients with endometriosis is enriched in activated macrophages, neutrophils, mast cells and pro-inflammatory cytokines including IL-6, TNF-α and IL-1 family mediators (Carvalho, J. C., et al; 2021). Autophagic flux is impaired in ectopic tissue and mTOR signaling is activated promoting survival in hostile, inflammatory conditions (Yuan, C. et al.; 2017; Jamali, N. et al.: 2021). Natural killer (NK) cell cytotoxicity is often reduced, impairing clearance of ectopic endometrial cells. B-cell activation and autoantibodies are also reported in some patients (Zondervan, K. T. et al.: 2018). This inflammatory milieu promotes nerve ingrowth, angiogenesis, pain sensitization and lesion persistence. Oxidative stress further amplifies that environment through iron-mediated reactive oxygen species and impaired antioxidant defenses. Turning what might have been a transient seeding of fragments into a chronic, self-perpetuating disease. (Agarwal, A., et al.; 2006; Jamali, N., et al.: 2021).

It is also essential to acknowledge neoangiogenesis and vascular remodeling as a key occurrence necessary in the development and recurrence of endometriosis. Endometriotic implants are highly vascularized with vascular endothelial growth factor (VEGF), matrix metallloproteinases (MMP-2 and MMP-9) and endothelin-1 being frequently upregulated. Providing ideal conditions for the survival of ectopic tissue. Emerging data also implicates neuroangiogenesis and aberrant innervation of lesions in the generation of pain with sensory and sympathethic fibers infiltrating endometriotic implants and interacting bidirectionally with inflammatory cells (Anaf V. et al., 2002; Asante A. & Taylor R. N., 2011).

Alongside these local tissue abnormalities studies suggest that a subset of women with endometriosis display systemic metabolic disturbances such as insulin resistance, hyperinsulinemia, obesity or concomitant polycystic ovary syndrome (PCOS) (Zhao L. et al.,

2016; Nie J. et al 2019; Zhang H. et al., 2023). These observations point towards a metabolic contribution to disease initiation and persistence and raise the possibility that modulating insulin signaling or energy metabolism might influence the progression of the disease (Zhang H. et al., 2023).

Metformin became relevant because it intersects with all theoretical levels at once. While it does not address retrograde menstruation directly it may weaken post-implantation survival conditions. AMPK activation can antagonize mTOR dependent growth signaling shifting the cells towards catabolic reactions, stress-responsive states, restore autophagy and limit inappropriate proliferation (Rena G. et al., 2017; Kimber-Trojan Ż. et al., 2022; Jamali N. et al., 2021). Inflammatory cytokine reaction may make the peritoneal environment less permissive while the anti-angiogenic effects may reduce lesion vascular support (Kimber-Trojan Ż. et al., 2022; Cheng, J. et al.; 2022). This multi-pathway alignment helps explain why metformin attracted more attention than many narrowly targeting compounds.

Pharmacology of Metformin: biologic rationale for metformin in endometriosis

Metformin is traditionally described as a glucose-lowering agent that reduces hepatic gluconeogenesis and increases peripheral glucose uptake. Yet the drug's pharmacology extends well beyond glycemic control and intersects with several pathways relevant to endometriosis (Kimber-Trojan Ż. et al., 2022).

Metformin activates AMPK which in turn inhibits mTOR complex 1 a key regulator of cellular growth and autophagy (Rena G. et al., 2017). In experimental models of endometriosis it reduces mTOR expression and restores autophagy-related markers such as Beclin-1 and Atg5 especially when combined with the polyphenolic antioxidant quercetin. These changes accompanied by reduced lesion cellularity and increased apoptotic activity suggests that modulation of autophagy is relevant in real life practices (Jamali N. at al., 2021).

Secondly it has impressive anti-oxidative and anti-inflammatory effects. Metformin enhances cellular antioxidant defenses including SOD activity and decreases markers of lipid peroxidation (Agarwal A. et al., 2006). In rodent models of endometriosis it has been proven to reduce levels of pro-inflammatory cytokines such as TNF-α and IL-6 while normalizing Nrf2 signaling (Jamali N. at al., 2021). These effects are consistent with a broad dampening of oxidative and inflammatory responses in the peritoneal cavity (Carvalho J. C. et al., 2021).

By improving insulin sensitivity and lowering circulating insulin and IGF-1 metformin also decreases growth-promoting signaling in hormone-responsive tissues (Nie J. et al., 2019; Barczyński B. et al., 2020). It's anti-inflammatory, anti-oxidative and anti-agiogenic properties

further undermine the necessary conditions that endometriotic lesions require (Kimber-Trojan Ż. et al., 2022). This convergence provides a strong theoretical basis for repurposing metformin in endometriosis treatment plans (Carvalho, J. C., et al; 2021; Zhang H. et al., 2023).

Metformin has been shown to reduce VEGF and MMP-9 levels and to modulate the endothelin-1/e-NOS axis (Cheng J. et al.; 2022). In women with endometriosis, treatment with metformin has been associated with decreased circulating endothelin-1 and improved e-NOS expression, suggesting that the drug can improve endothelial function and disrupt the vascular support of ectopic lesions (Biomedicines; 2022). These vascular effects align with a broader literature indicating that metformin improves endothelial function in diabetes, obesity and PCOS (Mather K. J. et al.; 2001; De Jager J. et al.; 2005).

Another important aspect of metformin's pharmacology are the anti-proliferative and pro-apoptotic properties. Evidence from endometrial and other gynecologic malignancies demonstrates that clinically used metformin doses can decrease proliferation markers and increase apoptotic indices in tumor tissue (Barczyński, B. et al.; 2020). Because endometriosis has been previously described as a benign neoplastic-like disorder, these anti-proliferative actions may be relevant to ectopic endometrial cells as well (Burney, R.O. & Giudice, L.C..; 2012).

Beyond these mechanistic domains, metformin is attractive from a clinical pharmacology perspective. It is orally administered, inexpensive and widely available with a long safety record in diverse populations including adolescents, women of reproductive age and older individuals. Gastrointestinal side effects are common but usually mild and transient, while serious adverse events such as lactic acidosis are rare and mainly associated with advanced renal, hepatic or cardiac disease (Rena, G. et al.; 2017). These characteristics make metformin a plausible candidate for long-term disease modification in a chronic condition like endometriosis.

However, pathway overlap is not the same as therapeutic proof. Many agents have shown anti-inflammatory or anti-angiogenic effects in experimental endometriosis without becoming clinically useful. A rigorous review must therefore ask whether the observed biological changes were measured in appropriate models, whether group allocation and variable control were credible and whether the inferential leap from lesion biology to symptom control was justified. That is the central methods question in the metformin literature.

Preclinical Evidence: Lesion Regression and Fertility Outcomes

Oner et al. provided one of the earliest direct tests of metformin in a rat model of surgically induced endometriosis. In this study uterine tissue has been transplanted to ectopic sites so that

implant size and histologic appearance can be measured after treatment. Afterwards the subjects were treated with metformin, letrozole or placebo for the control group and lesion response using morphologic criteria was assessed. This model is particularly useful because it standardizes lesion creation, treatment timing and tissue sampling. It has also been very successful at detecting changes in the lesion burden over a short interval under controlled conditions. Subjects treated with metformin showed reduction in size of ectopic implants in a dose-dependent manner with effects comparable to the aromatase inhibitor. Moreover, histologic analysis showed decreased cellular proliferation and increased signs of regression in metformin-treated lesions as well supporting a direct variant-lesion correlation (Oner G. et al., 2010).

Later experiments refined and extended these observations. Jamali et al. randomized multiple treatment pathways in rats with induced endometriosis including subjects receiving quercetin, metformin, both agents or control treatment. Methodologically this is stronger than a binary treated-versus-untreated design because it allows a partial assessment of independent and synergistic effects. It also reduces the risk that observed improvements are merely a generic feature of intervention or handling. Another important factor is that Jamali et al. did not rely on lesion size alone. Their endpoints included analysis of estradiol and TNF-α levels, oxidative stress markers and autophagy related proteins such as Beclin-1 and Atg5. Metformin alone was proven to reduce lesion size and improve estradiol and TNF-α levels while combination therapy achieved even greater results and produced the biggest normalization of oxidative stress and autophagy markers. These results suggest that metformin can act alone however may also serve as a component of rational combination regiment.

Several studies have focused on the issues surrounding angiogenesis within the lesions and extracellular matrix remodeling. In these models, metformin treatment reduced expression of VEGF and MMPs in ectopic tissue and increased the levels of metalloproteinases to ones corresponding to impairing neovascularization and vascular invasion (Cheng J. et al., 2022). Other studies compared metformin with letrozole and atorvastatin demonstrating that all three drugs triggered lesion apoptosis resulting in decreased size of the ectopic tissue, although through differing molecular pathways (Sapmaz T. et al., 2022). Together these experiments further prove the effectiveness of targeting non-hormonal pathways such as angiogenesis and inflammation can be highly effective in experimental endometriosis.

Preclinical work has also investigated fertility outcomes. In a mouse model of endometriosis metformin at doses lower than those used in diabetes reversed disease-associated subfertility. The treated animals had pregnancy rates similar to healthy control group subjects, along with

reduced lesion burden and less fibrosis and oxidative damage in ectopic sites (Neto A. C. et al., 2024). Conceptually, this is one of the strongest preclinical contrubions because fertility is closer to a clinically meaningful endpoint than lesion shrinkage alone. Another study showed that metformin improved endometrial receptivity markers such as leukemia inhibitory factor (LIF) and HOXA10 which are critical for successful implantation of embryo (Cheng J. et al., 2022). These findings bridge the gap between simple lesion regression and clinically meaningful outcomes such as embryo implantation and pregnancy.

Taken as a whole, preclinical studies present a remarkably consistent picture. Across independent laboratories and varied experimental designs metformin has been proven to reduce lesion area, normalize inflammatory and oxidative markers, improve endothelial functions and in several models restore impaired fertility. These convergent findings provide a strong foundation for clinical translation while also underscoring the need for human data.

Early Clinical Evidence and Systematic Reviews

Human data on metformin use in endometriosis remains limited but it is steadliy accumulating. One early clinical study treated women with laparoscopically confirmed endometriosis using metformin and studied changes in pain, fertility and angiogenic markers. Patients reported reductions in dysmenorrhea and chronic pelvic pain and an increase in pregnancy rates during follow-up. Biochemically VEGF levels decreased mirroring the anti-angiogenic effects seen in animal testing (Foda A. A. et al., 2012). Although the study was a non-randomized and open-label it provided an important proof-of-concept signal (Carvalho J.C. et al., 2021).

A systematic review in Frontiers in Medicine synthesized available preclinical and clinical data and concluded that in animal models, metformin consistently decreased lesion size and modified inflammatory, oxidative and angiogenic pathways. In humans, preliminary studies suggested symptom improvement and possible enhancement of fertility. However, the overall evidence was judged insufficient for firm clinical recommendations (Carvalho, J.C. et al.; 2021).

Narrative reviews such as Kimber-Trojnar et al. are useful for integrating mechanisms and framing the therapeutic rationale, but they are not substitutes for controlled data. Their strongest contribution is conceptual. They show why metformin continues to attract attention despite limited clinical proof. Their weakest aspect is that narrative synthesis can sometimes smooth over uneven methodological quality of the primary studies.

Beyond endometriosis, clinical experience with metformin in gynecologic oncology provides additional insights. In women with endometrial cancer, metformin has been associated with reduced tumor proliferation indices and in some observational cohorts improved survival

(Barczyński, B. et al.; 2020; Nevadunsky, N.S. et al.; 2014). A randomized trial in breast cancer patients on tamoxifen suggested that metformin might prevent or lessen endometrial thickening and improve insulin resistance without introducing significant gynecologic adverse effects (Davis, S.R. et al.; 2021). These studies do not prove efficacy in endometriosis. However, they do support the endometrial safety of chronic metformin therapy and reinforce its anto-proliferative potential in hormone-responsive tissues (Zhang, H. et al.; 2023).

Importantly, most clinical reports involve relatively short treatment durations and modest sample sizes. Long term adherence, patient-reported outcomes and comparative effectiveness against established hormonal regimens remain poorly characterized (Carvalho, J.C. et al.; 2021).

Positioning Metformin Among Current Therapeutic Options

At present, professional guidelines continue to recommend hormonal therapies and surgery as first-line treatments for endometriosis-associated pain and infertility (Dunselman, G.A.J. et al.; 2014). Within this framework, how should metformin be conceptualized?

Mechanistically, metformin differs from standard hormonal approaches in that it does not primarily act by suppressing ovarian estrogen production or ovulation (Nie, J. et al.; 2019). Instead, it modulates metabolic inflammatory, oxidative and vascular pathways that support lesion survival (Kimber-Trojan Ż. et al., 2022; Zhang, H. et al.; 2023). This distinctive mode of action makes metformin an attractive adjunct to hormonal therapy or potential standalone treatment in selected patient groups (Carvalho, J.C. et al.; 2021).

Particularly promising candidates include women with endometriosis coexisting with insulin resistance, metabolic syndrome, obesity or PCOS in whom metformin can address both reproductive and metabolic goals (Legro, R.S. et al.; 2007; Nie, J. et al.; 2019). Another group comprises women actively seeking pregnancy who wish to avoid or minimize ovulation-suppressing therapies. In such patients, metformin might offer symptom relief and possible fertility benefits without the contraceptive effects inherent to many hormonal regimens (Foda, A.A. et al.; 2012; Cheng, J. et al.; 2022).

Preclinical studies also support combination strategies. The synergy observed between metformin and quercetin, letrozole or atorvastatin in animal models suggests that future human regimens could integrate metformin into multi-drug protocols that simultaneously target multiple disease pathways (Oner, G. et al.; 2010; Jamali, N. et al.; 2021; Sapmaz, T. et al.; 2022). Conceptually, such multimodal regimens resemble current practice patterns in oncology, where agents with complementary mechanisms are combined to maximize benefits and prevent resistance (Barczyński, B. et al.; 2020; Ghadhab, I. et al.; 2022).

In summary rather than a direct competitor to existing therapies, metformin should currently be viewed as a promising adjunct and a targeted option for defined phenotypes, pending stronger evidence (Zhang, H. et al.; 2023).

Future directions and Research Gaps

When metformin literature is read through a methods-first lens a clear pattern emerges. The strongest evidence comes from controlled animal experiments in which lesions are induced in a standardized way, treatment exposure is defined and tissue endpoints are measurable. The clinical evidence is much weaker because sample sizes are small with the studies often non-randomized and outcome measures varying widely across reports. This pattern supports potential efficacy, but not established efficacy.

There is a need for adequately conducted randomized controlled trials. These trials should compare metformin with placebo as well as standard hormonal treatments, ideally in both pre and post-surgical populations. Many papers emphasize lesion size, histology, cytokines, VEGF, oxidative stress or receptivity markers. While these are valid and informative outcomes for mechanism-oriented work, they are not by themselves sufficient for clinical adoption. The decisive endpoints in women are pain reduction, quality of life, recurrence after treatment, spontaneous conception and live birth (Dunselman, G. A. J. et al.; 2014; Becker C. M. et al.; 2022). Future work must center those outcomes while retaining biomarker substudies for mechanistic interpretation.

Patient selection is another major gap. If metformin is most relevant through insulin signaling, AMPK activation, inflammatory modulation and anti-angiogenic effects benefits may be greatest in biologically selected populations. A stronger trial framework should begin with studies adopting phenotype-targeted designs. Given metformin's metabolic actions it is particularly important to determine whether women with insulin resistance, obesity or PCOS derive greater benefits than lean, metabolically healthy women with endometriosis (Legro R.S. et al.; 2007; Nie J. et al.; 2019). Yet current human studies rarely stratify by metabolic status, BMI, androgen profile, lesion subtype of molecular phenotype. Without such clarification a real therapeutic signal could be diluted in unselected samples (Zhang, H., et al.; 2023). Eligibility criteria should therefore be aligned with the mechanism being tested.

Future trials must explore optimal dosing, duration and timing. It is not yet clear whether standard diabetes doses are necessary for endometriosis or whether lower doses would suffice. The need for a continuous therapy versus a targeted one specific to the phases of the menstrual cycle should also be taken into account (Rena. G. et al.; 2017).

Moreover, long-term safety and oncologic surveillance are needed. While extensive experience in diabetes and cancer suggests that metformin is generally safe and may even be protective in some gynecologic malignancies, dedicated safety data in women with endometriosis especially regarding bone health, vitamin B12 levels and reproductive outcomes will be necessary if the drug is to be used over many years (Barczyński, B., et al.; 2020; Laskov, I., et al.; 2014; Davis, S. R., et al.; 2021; Ghadhab, I., et al.; 2022; Zhang, H., et al.; 2023).

Finally, future studies should build in methodological safeguards that are often weak or absent in the current literature: allocation concealment, blinded outcome assessment, explicit attrition handling and consistent long term follow-up. These features are routine in high-quality therapeutic trials and are necessary for metformin to be evaluated as more then an experimental adjunct.

Conclusion

The current literature supports metformin as a biologically plausible investigational therapy for endometriosis. Preclinical studies consistently show favorable effects on lesion burden and on inflammatory, oxidative, angiogenic, apoptotic and receptivity-related pathways (Oner, G. et al.; 2010; Jamali, N. et al.; 2021; Cheng, J. et al.; 2022, Neto, A.C. et al.; 2024). These studies are most persuasive when they include active comparators, multiple mechanistic endpoints and reproductive outcomes rather than lesion size alone.

Early human evidence, while limited, suggests benefits in pain reduction, cytokine profiles and possibly conception rates (Foda, A.A. et al.; 2012; Zhang, H. et al.; 2023). At the same time, the evidence base is not yet strong enough to consider metformin a fully established new treatment for endometriosis. The lack of large, well-controlled randomized trials, the heterogeneity of existing studies and uncertainties regarding optimal dosing, patient selection and long-term outcomes all argue for caution (Zhang, H. et al; 2023). For now, the most defensible vie is that metformin represents a highly promising investigational and off-label option, particularly suitable for women with combined endometriosis and metabolic dysfunctions as an adjunct to standard therapies (Nie, J. et al.; 2019; Zhang, H. et al.; 2023).

The correct interpretation of today’s literature is that metformin deserves continued investigation, because the mechanistic rationale is coherent and the experimental signal is consistent. The next step should not be broader rhetorical endorsement, but better trial design. If future randomized, phenotype-aware clinical trials confirm the benefits hinted at by current data, metformin may help shift endometriosis management towards a more integrated, metabolism-aware model (Zhang, H. et al.; 2023). In that scenario, metformin would no longer

be seen only as a diabetes drug, but as part of a broader therapeutic toolkit to address the inflammatory, vascular and metabolic dimensions of endometriosis while preserving reproductive potential (Kimber-Trojnar, Ż., et al; 2022; Becker, C.M. et al.; 2022).

Disclosure

Author's contribution

Conceptualization: and Karolina Bartkiewicz and Magdalena Papież and Anna Libera
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Funding Statement: This research has not received any special funding.
Institutional Review Board Statement: Not Applicable
Informed Consent Statement: Not Applicable
Data Availability Statement: Not Applicable
Acknowledgements: This research has not received any administrative or technical support.
Conflict Of Interest: The authors declare no conflict of interest.
All authors have read and agreed with the published version of the manuscript

In preparing this work, the author(s) used chatGPT for the purpose of AI-assisted refinements. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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