Review
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Off-Label Drug Use in Gynecology Evidence-Based Applications for Fertility and Pregnancy

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Abstract: Off-label drug use is common in women's reproductive healthcare, particularly when approved therapeutic options are limited, although the strength of supporting evidence varies substantially across drugs and indications. This narrative review aimed to synthesize and compare evidence on the off-label use of filgrastim, methotrexate, sildenafil citrate, misoprostol, letrozole, and pentoxifylline in fertility-, pregnancy-, and gynecology-related care. Relevant literature was identified from major biomedical databases and clinical trial registries and qualitatively synthesized according to study design, consistency of findings, clinical outcomes, safety findings, and methodological limitations. Methotrexate and letrozole showed comparatively well-established evidence for selected reproductive indications, particularly medical management of ectopic pregnancy and ovulation induction in women with polycystic ovary syndrome. Filgrastim and sildenafil demonstrated potential benefits for thin endometrium and implantation-related outcomes, although findings were heterogeneous and improvements in pregnancy outcomes were inconsistent. Misoprostol has extensive evidence-based reproductive and obstetric use despite variation in regulatory approval across settings. Pentoxifylline showed potential benefits for endometrial insufficiency and endometriosis-associated infertility, but evidence for sustained pregnancy and live-birth outcomes remains limited. Overall, off-label use in reproductive healthcare encompasses interventions with markedly different levels of evidentiary support. Appropriate prescribing should therefore consider evidence quality, indication-specific benefit–risk balance, patient selection, safety, and clinical monitoring.

Introduction

Off-label prescribing refers to the use of a medicine outside its approved labeling, including differences in indication, dosage, route of administration, formulation, or patient population. In contemporary healthcare practice, off-label use is common in fields where approved therapeutic options remain limited or where clinicians face complex conditions that require individualized treatment decisions (1). This practice is particularly relevant in women's reproductive healthcare, where therapeutic needs in fertility, pregnancy, and gynecologic disorders are not always fully addressed by licensed indications. Off-label prescribing is often employed when effective approved therapies are limited or unavailable, thereby expanding treatment options and helping to address unmet clinical needs. However, such use also raises important concerns regarding efficacy, safety, ethical justification, and rational prescribing, while posing challenges for healthcare providers, patients, and health insurance systems (2, 3).

Off-label drug use can offer significant therapeutic benefits and address unmet medical needs, yet it also raises questions about efficacy, safety, and ethical considerations. This duality highlights the importance of careful evaluation and documentation in clinical practice. Eguale *et al.*, (2016) has found association between off-label drug use and adverse drug events (ADEs) in adults. The research indicates that while off-label use can address unmet medical needs, it also carries risks, particularly when lacking strong scientific evidence. However, when off-label use is supported by strong scientific evidence, the risks are similar to those of on-label use, suggesting that careful evaluation and documentation in clinical practice are crucial (4). Another study reviewed the comparative effectiveness and safety of various pharmacological interventions, including off-label uses, and found that off-label medications can sometimes be more favorable than approved treatments based on specific criteria evaluated in RCTs. This indicates that off-label drugs, when supported by robust clinical evidence, do not inherently carry systematic risks (5).

Off-label prescribing in reproductive healthcare also requires careful clinical and ethical consideration, particularly when treatment involves women who are

pregnant or planning pregnancy. In clinical practice, patients should be informed when a medicine is being used outside its approved indication and should receive appropriate information regarding the expected benefits, uncertainties, available alternatives, and potential maternal or fetal risks. Such discussion supports shared decision-making and appropriate clinical documentation.

Most available studies and reviews focus on single drugs, specific interventions, or narrow clinical indications. Some medications, such as methotrexate and letrozole, already have relatively strong evidence for selected reproductive applications, whereas others, including filgrastim, sildenafil citrate, and pentoxifylline, remain supported by heterogeneous and still evolving evidence (6, 7, 8, 9, 10). Misoprostol occupies a distinctive position because of its extensive practical use in reproductive care despite regulatory variation across settings (11). As a result, the literature provides important findings, but it does not always offer an integrated picture of how these off-label agents compare in terms of clinical application, safety profile, and implications for healthcare practice.

This gap is important because off-label prescribing in women's reproductive healthcare should not be assessed solely on the basis of therapeutic potential, but also in relation to evidence quality, patient safety, and the need for careful clinical judgment. A more integrated review is therefore needed to synthesize the available evidence across key off-label drugs used in fertility- and pregnancy-related care. This article aims to explore the using of off-label drug use in gynecology through a literature review. By examining specific instances of off-label prescribing, we seek to understand the factors that influence these decisions, the outcomes for patients, and the broader implications for clinical practice and policy. This review will provide insights into how gynecologists navigate the complexities of off-label drug use and contribute to the ongoing discussion about its place in modern medicine. A comprehensive summary of the primary indications, off-label reproductive uses, evidence strength, and safety profiles for each evaluated agent is presented in **Supplemental Table 1**.

Methodology

Literature Search Strategy

A thorough narrative literature search was systematically conducted to identify all relevant, high-quality studies published in English up to October 26, 2024. Literature was comprehensively retrieved from major biomedical databases and clinical trial resources, including MEDLINE, Scopus, Embase, ScienceDirect, the Cochrane Library, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, the EU Clinical Trials Register, and the World Health Organization International Clinical Trials Registry Platform. Search terms were meticulously centered on off-label or repurposed drug use across key areas in gynecology and reproductive medicine, specifically including infertility, endometrial disorders, recurrent pregnancy loss, and the selected therapeutic drugs filgrastim, methotrexate, sildenafil citrate, misoprostol, letrozole, and pentoxifylline. Additionally, reference lists of relevant articles and review papers were thoroughly examined to identify any potential additional pertinent publications (12).

Study Selection and Eligibility Criteria

Studies were considered eligible if they addressed the off-label use of filgrastim, methotrexate, sildenafil citrate, misoprostol, letrozole, or pentoxifylline for gynecologic or reproductive indications. Randomized controlled trials, non-randomized controlled studies, cohort studies, case-control studies, large case series, systematic reviews, and meta-analyses were considered where relevant to the clinical question. Study selection was conducted independently by two authors based on relevance to the scope of the review, clinical applicability, and contribution to the evaluation of efficacy, safety, dosing, or therapeutic use. Any differences in study selection were resolved through discussion between the two authors.

Synthesis and Evaluation of Evidence

Given the substantial heterogeneity in study designs, patient populations, clinical indications, interventions, and reported outcomes, a narrative synthesis was considered more appropriate than a formal quantitative or systematic synthesis. The included literature was evaluated qualitatively according to study design, consistency of findings, clinical relevance, reported efficacy and safety outcomes, and important methodological limitations. Greater interpretive weight was given to systematic reviews, meta-analyses, and randomized controlled trials, while observational studies and case series were used to provide additional clinical context where higher-level evidence was limited. The purpose of the synthesis was to provide a comprehensive and clinically oriented comparison of the available evidence across the selected drugs rather than to perform statistical pooling or formal risk-of-bias assessment.

Evidence Synthesis of Off-Label Drugs in Gynecology

Filgrastim

Mechanism of Action

Filgrastim (NEUPOGEN) is a short-acting recombinant human granulocyte colony-stimulating factor (G-CSF) that induces the proliferation and differentiation of neutrophil progenitor cells and promotes the release of neutrophils from the bone marrow into the circulation (13).

Approved Indications

The US FDA has approved filgrastim for six major indications: (1) prevention of febrile neutropenia (FN) in chemotherapy-induced neutropenia (CIN), (2) reduction of fever duration and time to neutrophil recovery in patients with acute myeloid leukemia (AML) undergoing induction or consolidation chemotherapy, (3) minimization of fever duration and time to neutrophil recovery in AML patients receiving similar regimens, (4) mobilization of peripheral blood progenitor cells (PBPC) for collection and transplantation, (5) reduction in the duration of neutropenia and associated complications in patients undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) or those with non-myeloid malignancies, and (6) enhancement of survival in patients acutely exposed to myelosuppressive levels of radiation, such as in acute radiation syndrome (13).

Off-Label Applications in Reproductive Medicine

Beyond its hematological indications, granulocyte colony-stimulating factor has gained attention in reproductive medicine for its potential to enhance implantation and reduce unexplained recurrent pregnancy loss. Patent data and preclinical observations have suggested that G-CSF may positively influence cases of implantation failure and repeated pregnancy loss, possibly through effects on the endometrium (14, 15). G-CSF also affects endometrial thickness (16), modulate the activity of human decidual macrophages, influence ovulation and overall ovarian function, enhance ovarian stimulation in poor responders, act as a biomarker for oocytes and embryos with higher implantation potential, contribute to the development of early endometriotic lesions, and suppress autoimmune responses that may impair fertility (17). It has also been implicated in the development of preantral follicles within the ovaries (18).

Clinical Evidence

The clinical evidence on filgrastim's efficacy in gynecology is promising but heterogeneous. Gleicher *et al.* (2013) reported that intrauterine administration of G-CSF significantly increased endometrial thickness and was associated with a notable rise in clinical pregnancy rates, with only a single case of ectopic pregnancy observed (19). Similarly, Aleyasin *et al.* (2016) demonstrated a considerable increase in implantation rates among women with recurrent IVF failures who received G-CSF treatment (34). Kalem *et al.* (2020) provided further support, showing that G-CSF administration led to higher pregnancy rates, even in cases where endometrial thickness did not increase, suggesting that immunomodulatory mechanisms may be involved beyond endometrial proliferation alone (35). Contrasting these findings, Barad *et al.* (2014) found no significant improvement in IVF outcomes following intrauterine G-CSF perfusion, particularly among younger women, highlighting the possibility that the benefit of G-CSF may be limited to select patient populations or specific clinical scenarios (16).

Dosing and Administration

Currently, there is no consensus on the optimal dosing or administration protocol for filgrastim in gynecology. Most studies report intrauterine infusion as the preferred route, but the dosage, timing, and frequency vary considerably, underscoring the need for standardized protocols based on prospective, comparative trials. Regarding safety, filgrastim is generally well tolerated in reproductive applications. Adverse effects in this context are rare and mild, in contrast to the systemic side effects such as bone pain and leukocytosis observed when used for hematological indications (13).

Recent randomized controlled trials and meta-analyses have adopted a standard intrauterine dose of 300 µg filgrastim (Neupogen® or biosimilar) in 1 mL, typically administered when endometrial thickness remains < 7 mm after estrogen priming, often 24–72 hours before embryo transfer (Kalem *et al.*, 2020; Xie *et al.*, 2017; Jain *et al.*, 2018). Repeat dosing after 48–72 hours has been described if thickness remains suboptimal (20). This protocol has been shown to improve pregnancy outcomes in several trials, although the degree of benefit varies across studies. For example, Kalem *et al.* (2020) observed increased pregnancy rates with intrauterine G-CSF even without significant increases in endometrial thickness, suggesting immunological mechanisms may contribute (35). A recent cohort study also supports the benefit of this approach for women with recurrent implantation failure (8). However, other well-designed RCTs report no significant difference in pregnancy rates (20), highlighting the need for further large, multicenter trials to standardize protocols and clarify indications.

Safety and Adverse Effects

Filgrastim is generally well tolerated in reproductive applications, with rare and mild adverse effects. This contrasts with the systemic side effects seen in hematological indications, such as bone pain and leukocytosis (13).

Summary and Research Gaps

In summary, filgrastim (G-CSF) represents a novel and potentially valuable off-label intervention for selected women experiencing thin endometrium or recurrent implantation failure, with a plausible biological rationale and encouraging, though mixed, clinical evidence. The lack of standardized dosing regimens, heterogeneity in patient selection, and limited large-scale randomized studies constitute important research gaps. Further well-designed trials are warranted to define its efficacy, safety, and the specific patient populations most likely to benefit from G-CSF therapy in reproductive medicine.

Methotrexate

Methotrexate is a synthetic analogue of folic acid that functions as a competitive inhibitor of folate-dependent enzymes, thereby impeding DNA synthesis in rapidly dividing cells (21). Initially developed in 1949, methotrexate was designed to compete with folic acid and inhibit cell replication. Its first clinical use was in the treatment of acute lymphoblastic leukemia, but its effectiveness against choriocarcinoma was discovered serendipitously, prompting further investigation into its role in other trophoblastic tissue disorders (6).

Methotrexate is authorized by the FDA for the treatment of neoplastic disease, psoriasis, and rheumatoid arthritis (37). Methotrexate is currently a prominent chemotherapeutic option utilized to treat a wide range of cancer varieties. Patients with inflammatory bowel disease, vasculitis, psoriasis, systemic lupus erythematosus, and numerous other connective tissue disorders can also safely and effectively utilize this medication (38).

Off-label Applications in Gynecology

The application of methotrexate in gynecological practice was limited to the treatment of malignancies until 1982, when the initial documentation of its use to manage an interstitial pregnancy emerged. Since then, the administration of methotrexate for the treatment of tubal, cervical, and interstitial pregnancies has gained extensive recognition and implementation (22). Furthermore, methotrexate has been employed in the treatment of placenta accreta and pregnancies implanted within a uterine scar and for treat ectopic pregnancy (39). Its use for the medical management of ectopic pregnancy has

become routine, due to evidence that medical therapy reduces morbidity and costs relative to surgery, while preserving future fertility potential (40).

Clinical Evidence

Randomized controlled trials and cohort studies have confirmed methotrexate's efficacy in resolving ectopic pregnancies. Notably, Yamaguchi *et al.* (2022) found that a single local injection of methotrexate was safe and effective for the treatment of cesarean scar pregnancy, regardless of fetal cardiac activity or initial hCG levels, and may allow for subsequent uneventful pregnancies (39). The single-dose regimen is frequently employed, with studies demonstrating successful resolution rates and substantial reductions in treatment-related costs compared to surgical interventions (23).

Dosing and Administration

For ectopic pregnancy, the most commonly used protocol is a single intramuscular injection of methotrexate at a dose of 50 mg/m^2 body surface area. Alternative protocols, such as multi-dose regimens, may be used in select cases but are associated with increased risk of toxicity and require more intensive monitoring (21).

Safety and Adverse Effects

The toxicity commonly associated with methotrexate therapy arises from its ability to inhibit folate, which in turn affects other quickly dividing normal cells in a non-selective manner. Tissues with a high rate of cellular regeneration, such as hair follicles, the gastrointestinal tract lining, and bone marrow, are particularly susceptible. Exposure to methotrexate for ectopic pregnancy, although involving shorter durations and slightly lower doses compared to other non-gynecologic uses, can still cause adverse effects in women. These effects may include nausea, vomiting, loss of appetite, diarrhea, inflammation of the mouth, hair loss, increased liver enzymes, lung scarring, and abnormalities in blood cells (21). Due to the potential dangers linked to these negative responses, both the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine have identified immunodeficiency, harm to organs responsible for metabolizing methotrexate, or pre-existing conditions that may worsen due to an adverse reaction as conditions where methotrexate therapy should not be used (21).

Summary and Research Gaps

In summary, methotrexate is a well-established, evidence-based medical therapy for ectopic pregnancy and other selected gynecologic conditions. Its clinical advantages include high efficacy, cost-effectiveness, and fertility preservation. However, careful patient selection, appropriate dosing, and vigilant monitoring are required to minimize toxicity, and its use is contraindicated in certain high-risk populations. Ongoing research may further refine its indications and optimize patient outcomes (6, 39).

Sildenafil Citrate

Sildenafil citrate is a selective phosphodiesterase type 5 (PDE5) inhibitor. Its principal mechanism involves inhibition of PDE5, which increases intracellular levels of cyclic guanosine monophosphate (cGMP) in response to nitric oxide (NO) release. This cascade results in smooth muscle relaxation and vasodilation, leading to enhanced blood flow to target tissues (24). In the context of gynecology, the discovery of endothelial and inducible nitric oxide synthase isoforms in the endometrium and myometrium provided the biological basis for exploring sildenafil's effects on uterine perfusion (41). Sildenafil is FDA-approved for the treatment of male erectile dysfunction and pulmonary arterial hypertension (24).

Off-label Applications in Gynecology

Off-label, sildenafil has been investigated for its potential to improve endometrial thickness, uterine perfusion, and endometrial receptivity in women with a thin endometrium—a factor associated with reduced implantation and pregnancy rates in ART. Its vasodilatory and possible immunomodulatory effects have also led to studies exploring its use in recurrent implantation failure, infertility related to poor endometrial response, and certain ovulation induction protocols (9, 25).

Clinical Evidence (key Rcts/meta-analyses and Main Findings)

Early pilot studies and subsequent research demonstrated that intravaginal sildenafil could enhance endometrial proliferation in women with recurrent IVF failure due to insufficient endometrial thickness (25). Takasaki *et al.* (2010) found that intravaginal sildenafil (100 mg/day) significantly improved uterine blood flow and endometrial thickness in women with thin endometrium (42).

A randomized controlled trial by Firouzabadi *et al.* (2011) compared sildenafil (50 mg/day) to estradiol in women with poor endometrial response. The sildenafil group showed significantly greater endometrial thickness and a higher frequency of triple-line endometrial patterns, though the differences in implantation and chemical pregnancy rates did not reach statistical significance (43).

Kortam *et al.* (2018) reported that adjunctive oral sildenafil (25 mg every 8 hours) with hormone therapy in clomiphene cycles improved endometrial thickness and morphology, and modestly increased pregnancy rates (44). However, Barad *et al.* (2014) and Marin *et al.* (2021) both documented that while endometrial thickness improved, this did not consistently translate into higher clinical pregnancy rates, particularly in IVF and IUI cycles. Marin *et al.* (2021) found benefits mainly in timed intercourse cycles, suggesting that efficacy may depend on cycle type and the underlying angiogenic state of the endometrium (9, 16).

Recent systematic reviews and meta-analyses further clarify sildenafil's role in infertility management. Li *et al.* (2020) analyzed multiple RCTs and found that sildenafil significantly increased endometrial thickness (mean difference ~1.43 mm) and improved clinical pregnancy rates (relative risk 1.75) in women with thin endometrium, with no significant increase in miscarriage risk (45). Similarly, Marin *et al.* (2021) conducted a meta-analysis including over 1,200 women and demonstrated that sildenafil, whether administered orally or vaginally, increased endometrial thickness by an average of 1.25 mm and improved clinical pregnancy rates, particularly in timed intercourse and frozen embryo transfer cycles. The

Table 1. Pharmacological profile and clinical applications of sildenafil in reproductive health.

Aspect	Details	References
Mechanism of Action	Inhibits PDE5 → ↑ cGMP → ↑ nitric oxide → smooth muscle relaxation → improved uterine blood flow. May reduce natural killer (NK) cell activity and enhance endometrial tolerance to embryos.	(25, 9, 45, 27)
Approved Use	Treatment of male erectile dysfunction (FDA-approved).	(24)
Off-Label Applications	- Enhancing endometrial thickness in infertility treatments (e.g., thin endometrium). - Adjunct therapy in IVF, IUI, and timed intercourse cycles.	(26, 9, 43, 44, 45)
Clinical Outcomes	Positive Effects: - ↑ Endometrial thickness - ↑ Uterine blood flow - Improved pregnancy rates in timed intercourse Conflicting Evidence: - Inconsistent IVF outcomes	(17, 26, 9, 43, 44, 45)
Dosage & Administration	- 25–100 mg/day (oral or intravaginal). - Common regimens: Daily from cycle day 1 until progesterone initiation or every 8 hours post-cycle day 2	(9, 43–45)
Safety	Generally well-tolerated. Mild side effects (e.g., headache, flushing). No severe adverse events reported.	Not explicitly stated
Key Studies	- Vaginal sildenafil improved endometrial proliferation in IVF failure cases. - Significant endometrial thickening vs. estradiol. - Benefits limited to timed intercourse. - Inconsistent IVF pregnancy rates.	(26, 9, 43, 44, 17)
Proposed Mechanisms	- Immunomodulation (↓ NK cell activity). - Enhanced estrogen-induced endometrial growth. - Improved angiogenesis and endometrial receptivity.	(9, 45, 27)

benefit was less pronounced in IVF or IUI settings (9). A more recent systematic review by Baradwan *et al.* (2023) corroborated these results, showing that sildenafil used as an adjuvant during the luteal phase increased endometrial thickness and clinical pregnancy rates, regardless of administration route, without raising the risk of adverse effects (46). These findings reinforce the potential value of sildenafil as an adjunct for thin endometrium in selected patient populations but also underscore the need for large-scale, well-designed RCTs to determine optimal protocols and patient selection.

Dosing and Administration (including Protocols)

Both oral and intravaginal routes have been investigated, with variation in dosing, timing, and treatment duration across studies. Common regimens are summarized in **Table 1**. Sildenafil is generally initiated during the follicular phase and continued through ovulation or embryo transfer, particularly in women with thin endometrium, and may be used in combination with estrogen or other ovulation-induction therapies (9, 35, 34).

Safety and Adverse Effects

Sildenafil is generally well-tolerated at doses used in gynecology. Reported adverse effects include headache, flushing, nasal congestion, and, rarely, hypotension or visual disturbances. Serious complications are rare at therapeutic doses, but caution is warranted in patients with cardiovascular risk factors (24).

Sildenafil citrate offers a promising off-label approach to managing thin endometrium, especially in timed intercourse cycles, with evidence for improved endometrial thickness and blood flow. However, its impact on implantation and live birth rates remains inconsistent, particularly in ART settings such as IUI and IVF. Proposed mechanisms—beyond vasodilation—include immunomodulation, estrogen synergy, and angiogenic modulation, but these require further elucidation. Current evidence does not support routine use in all infertility contexts. Well-powered, phase-specific RCTs are needed to define patient selection, optimal protocols, and long-term safety, as well as to clarify the mechanism of action in endometrial remodeling (9, 26, 43).

Misoprostol

Misoprostol, a synthetic prostaglandin E1 (PGE1) analog (40, 41) is approved globally for the prevention and treatment of nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers (11). Its structural similarity to endogenous prostaglandins enables interaction with prostaglandin receptors, mimicking physiological effects such as uterine contraction, cervical ripening, and modulation of inflammatory responses. Prostaglandins (PGs), particularly PGE2, are critical mediators of reproductive processes, including ovulation, luteolysis, pregnancy maintenance, and parturition (48).

Misoprostol is globally approved for the prevention and treatment of NSAID-induced gastric ulcers (11). Despite this, its robust uterotonic properties have led to widespread off-label use in reproductive medicine, and it is included in the WHO Model List of Essential Medicines for multiple gynecological and obstetric indications (49).

Off-label Applications in Gynecology

Off-label, misoprostol is used extensively for induction of labor, cervical ripening before surgical procedures, medical management of miscarriage and abortion, and prevention and treatment of postpartum hemorrhage (PPH) (27). Its stability at room temperature, affordability, and ease of administration make it especially valuable in resource-limited settings and for pre-induction cervical preparation (50).

Clinical Evidence (Key RCTs/Meta-analyses and Main Findings)

First synthesized in 1973, misoprostol has become a cornerstone for labor induction and cervical ripening due to its stability, affordability, and ease of administration. Unlike heat-sensitive prostaglandins, misoprostol is effective in low-resource settings, offering a practical

alternative for pre-induction cervical preparation (50). Cochrane reviews and meta-analyses highlight its superior efficacy over oxytocin and dinoprostone in reducing oxytocin augmentation needs and cesarean rates, while maintaining safety (27). Misoprostol is also effective for incomplete abortion, medical abortion (alone or with mifepristone), and cervical priming before surgical abortion. Its administration expedites delivery in maternal or fetal compromise (e.g., hypertensive disorders, infection), and it plays a significant role in PPH prevention and treatment, especially when oxytocin is unavailable (51).

Despite not being the first-line agent for labor induction in many guidelines, existing evidence substantiates its efficacy and cost-effectiveness, although standardized dosing regimens and formal obstetric approval remain lacking (27). Additional research has indicated prostaglandins (including misoprostol) may support fertility through several mechanisms—enhancing myometrial contractility, promoting sperm-oocyte binding, relaxing the isthmic tube, supporting the luteal phase, and immune modulation (52). *In vivo* studies in humans suggest that vaginally administered prostaglandins improve sperm passage through cervical mucus and increase uterine contractility, thereby enhancing the chances of conception (47). PGE1 administered intravenously also increases non-pregnant uterine contractility, facilitating sperm migration to the fallopian tubes. Furthermore, embryo-derived PGE has been shown to mediate embryo transport in animal models, emphasizing its physiological significance for fertility (48).

Dosing and Administration (Including Protocols)

Misoprostol can be administered orally, vaginally, buccally, or sublingually.

- For labor induction: Common regimens include 25–50 mcg vaginally every 4–6 hours (27)
- For medical abortion: 800 mcg vaginally or buccally every 3–12 hours, depending on gestational age and clinical protocol (28)
- For PPH: 600–800 mcg orally or sublingually immediately after delivery if oxytocin is unavailable (51).

Dosing for fertility-related applications is not standardized and largely extrapolated from labor induction protocols.

Safety and Adverse Effects

Misoprostol is generally well-tolerated; most side effects are dose-dependent and include shivering, pyrexia, diarrhea, and abdominal pain. Rare but serious complications can include uterine hyperstimulation or rupture, especially with high or frequent dosing in labor induction (27). Data on long-term fetal or maternal safety in repeated exposures remain sparse, underscoring the need for continued monitoring and research.

Summary (Clinical Value, Limitations, Research Gaps)

Misoprostol is a cornerstone drug in global reproductive healthcare due to its efficacy, affordability, and ease of storage. Its proven value in labor induction, abortion care, and PPH management is reflected in its inclusion in WHO guidelines. However, regulatory barriers and lack of formal approval for obstetric uses in some countries, as well as variability in dosing protocols and insufficient long-term safety data, remain significant challenges. Large-scale, randomized trials and harmonized guidelines are needed to optimize protocols and expand safe access (27, 49, 51).

Letrozole

Letrozole is a third-generation nonsteroidal aromatase inhibitor (AI) that acts by reversibly binding to the cytochrome P450 aromatase enzyme, the rate-limiting step in estrogen biosynthesis. This inhibition prevents the conversion of androgens (testosterone, androstenedione) to estrogens (estradiol, estrone), resulting in suppressed systemic estrogen levels (7, 53). Lower estrogen concentrations alleviate negative feedback on the hypothalamic-pituitary-ovarian (HPO) axis, thus increasing gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone (FSH) secretion, and promoting ovarian follicular development (29). Unlike clomiphene citrate, letrozole does not deplete estrogen receptors or have antiestrogenic effects on the endometrium or cervical mucus, thereby preserving endometrial receptivity (49, 50).

Letrozole is licensed for extended adjuvant therapy in postmenopausal women with early-stage, hormone receptor-positive breast cancer, as well as first- and second-line treatment for advanced or metastatic hormone receptor-positive breast cancer (55).

Off-label Applications in Gynecology

Off-label, letrozole is widely used for ovulation induction in women with anovulation or polycystic ovary syndrome (PCOS), ovarian stimulation for intrauterine insemination (IUI) and *in vitro* fertilization (IVF), and for fertility preservation strategies (7, 49).

Clinical Evidence (Key RCTs/Meta-analyses and Main Findings)

Letrozole has robust evidence supporting its use in ovulation induction and assisted reproductive technology (ART). In a large multicenter RCT, letrozole led to higher ovulation and live birth rates compared with clomiphene in women with PCOS (ovulation: 61.7% vs. 48.3%; live birth: 27.5% vs. 19.1%) (56). Begum *et al.* (2009) similarly found higher ovulation rates (62.5% vs. 37.5%) and greater endometrial thickness with letrozole than clomiphene in women with previous clomiphene failure (57). Meta-analyses confirm that letrozole is associated with increased clinical pregnancy and live birth rates, improved endometrial thickness, and lower rates of multiple gestations compared to clomiphene (54, 52). In ART, letrozole is used for mild ovarian stimulation to reduce the risk of ovarian hyperstimulation syndrome (OHSS) and improve endometrial receptivity, though high-quality data in this context remain more limited (7, 50).

Dosing and Administration (Including Protocols)

- Standard Regimen: 2.5–7.5 mg/day for 5 days, typically starting on cycle day 2 or 3 (29)
- High-Dose Protocols: reported that doses up to 12.5 mg/day may benefit women unresponsive to standard dosing, without compromising endometrial thickness.

- Extended Courses: Newer studies suggest starting at 5 mg/day or using a 10-day course can improve ovulation rates and shorten time to conception.
- In ART, letrozole may be combined with gonadotropins for mild stimulation or used in the luteal phase to reduce circulating estradiol and decrease OHSS risk (54).

Safety and Adverse Effects

Letrozole is generally well-tolerated. The most common adverse effects are mild and include fatigue, dizziness, and headache (56). At doses up to 5 mg/day, side effect rates are similar to placebo (57). Unlike clomiphene, letrozole does not adversely affect endometrial quality or cervical mucus, nor does it exacerbate vasomotor symptoms (49, 52). Large-scale studies have not shown an increased risk of congenital malformations or adverse perinatal outcomes compared to clomiphene or natural conception (30).

Summary (Clinical Value, Limitations, Research Gaps)

Letrozole represents a paradigm shift in ovulation induction, offering superior pregnancy rates and endometrial receptivity with fewer side effects than clomiphene citrate. Its short half-life and lack of estrogen receptor downregulation allow rapid clearance, preserving late follicular phase endometrial development (29). Letrozole's role in mild ovarian stimulation, ART, and fertility preservation continues to expand, but unresolved issues include optimal dosing for diverse populations, long-term safety, and its efficacy in non-PCOS infertility (7). Large, well-designed RCTs are warranted to further refine protocols and expand its indications.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative and non-selective phosphodiesterase (PDE) inhibitor. By reducing plasma viscosity and enhancing erythrocyte and leukocyte flexibility, it improves blood rheology and tissue oxygenation. Pentoxifylline also suppresses platelet aggregation and neutrophil adhesion, thereby promoting microcirculatory flow. These properties support its approved use as a hemorheologic agent (31). Pentoxifylline is FDA-approved for the treatment of intermittent claudication in patients with chronic occlusive peripheral vascular disease. While effective for symptom relief, it is not considered a substitute for surgical or definitive vascular interventions (58).

Off-label Applications in Gynecology

Interest in pentoxifylline's utility in reproductive medicine has grown, especially in cases of endometrial insufficiency and endometriosis. Early and recent clinical studies suggest benefits in improving endometrial thickness, oocyte yield, embryo quality, and serum estradiol levels during ovarian stimulation in IVF cycles (32). Combination therapy with tocopherol (vitamin E) appears to enhance endometrial thickness and pregnancy rates, especially in women with thin endometrium post-radiation (58, 59). Pentoxifylline has also been evaluated in the management of endometriosis-related infertility, often in combination with metformin, showing efficacy in reducing endometrioma size, pain, and inflammatory markers, although effects on pregnancy rates are less clear (60, 63).

Clinical Evidence (Key RCTs/Meta-analyses and Main Findings)

Clinical evidence supports pentoxifylline's ability to improve endometrial parameters. Vitale *et al.* (2022) reported improved endometrial thickness, oocyte yield, embryo quality, and serum estradiol levels during ovarian stimulation in IVF cycles (32). Bataille *et al.* (2002) and Aleyasin *et al.* (2009) both demonstrated that pentoxifylline, when combined with vitamin E, enhanced endometrial thickness and pregnancy rates, especially among women with prior radiation exposure or thin endometrium (59, 60).

A randomized controlled trial by Lasker *et al.* (2024) compared metformin alone to metformin plus pentoxifylline in women with symptomatic endometrioma, finding that the combination more effectively reduced endometrioma size, pain, and IL-6 levels, although pregnancy rates did not differ significantly (61). Similarly, Creus *et al.* (2008) found a higher cumulative pregnancy rate at six months after laparoscopic surgery in patients receiving pentoxifylline compared to placebo (62).

A recent systematic review concluded that pentoxifylline, alone or in combination with antioxidants, may improve endometrial perfusion and receptivity, but high-quality data on live birth outcomes remain insufficient (10).

Dosing and Administration

- Standard regimen: Pentoxifylline is typically administered orally at 400 mg two or three times daily in vascular indications; for fertility or endometrial indications, protocols vary widely (32).
- Combination regimens: Studies often combine pentoxifylline with vitamin E (tocopherol 1,000 IU/day) or metformin (60, 63, 59).
- Duration: Treatment duration in reproductive studies ranges from several weeks up to three months, but no consensus protocol exists.

Proposed Mechanisms in Fertility

1. Oxidative Stress Mitigation: Protects embryos from hydrogen peroxide (H2O2)-induced lipid peroxidation, improving IVF outcomes (60).
2. Immunomodulation: Pentoxifylline augments blood circulation by enhancing the flexibility of erythrocytes and leukocytes. It also inhibits the aggregation of platelets (31). Another investigations, indicate that immunological pathways have a role in the pathophysiology of endometriosis-related reproductive failure. Substantial data from animal models indicates that immunomodulation, via various non-specific immunomodulators such pentoxifylline, influences both the formation of endometriotic implants and infertility associated with endometriosis. Based on this clinical and experimental evidence, and given the failure of all other therapy modalities, it is imperative that prospective trials of immunological therapies be conducted promptly (63).

1. Enhanced Endometrial Perfusion: Improves microvascular blood flow, supporting endometrial receptivity (33).

Safety and Adverse Effects

Pentoxifylline is generally well-tolerated, with most adverse effects being mild gastrointestinal symptoms (nausea, dyspepsia, diarrhea) and headache. Serious adverse reactions are rare. No increase in adverse pregnancy or perinatal outcomes has been documented in fertility studies to date (32, 31). Nevertheless, long-term safety and teratogenicity data remain limited.

Summary (Clinical Value, Limitations, Research Gaps)

Pentoxifylline offers potential as an adjunct therapy for endometrial insufficiency and endometriosis, especially when used in combination with antioxidants or metabolic agents. Its dual hemorheologic and immunomodulatory actions are mechanistically attractive, and available data suggest improvements in endometrial thickness, embryo quality, and inflammatory status. However, benefits for live birth and ongoing pregnancy rates remain inconsistent. The lack of standardized dosing, variable results across studies, and the need for further high-quality RCTs and meta-analyses represent key gaps. Future research should clarify optimal regimens, long-term safety, and its specific indications within infertility management (32, 63).

Comparative Interpretation of the Evidence

The evidence that is currently available indicates that the intensity, consistency, and clinical maturity of off-label drug use vary significantly among the six agents currently under review. The most established evidence supports the use of methotrexate and letrozole for specific reproductive indications. The medical management of appropriately selected ectopic pregnancies is well-defined by methotrexate, which is supported by established treatment protocols and substantial clinical experience (6), (21), (22)-(23). Letrozole is similarly supported by systematic reviews and randomized controlled trials, which have shown favorable ovulation, clinical pregnancy, and live-birth outcomes, particularly in women with polycystic ovary syndrome (7), (29), (54), (56), (30). Consequently, these agents are off-label applications for which the clinical use and evidence base are relatively well-developed.

Conversely, filgrastim and sildenafil citrate exhibit promising but inconsistent evidence. Filgrastim has shown potential benefits in women with thin endometrium or recurrent implantation failure; however, the absence of standardized treatment protocols, variables in patient selection, and conflicting trial results limit the ability to draw firm conclusions about its routine use (8, 13, 16, 19–23). The surrogate improvements in endometrial thickness and uterine perfusion that Sildenafil has consistently demonstrated have not consistently translated into improved implantation, clinical pregnancy, or live-birth outcomes across assisted reproductive technology settings (9, 33–38). As a result, the available evidence does not support the routine use of both agents across all infertility populations, despite the potential value they may have in carefully selected patients.

Misoprostol is in a unique position due to the fact that several of its reproductive and obstetric applications are already well-established in clinical practice, despite the fact that regulatory approval levels vary across jurisdictions. It is supported by evidence for the prevention or treatment of postpartum hemorrhage, management of miscarriage and medical abortion, labor induction, and cervical ripening (11, 40, 43–47). Its established clinical importance in reproductive healthcare is further reflected in its inclusion in the WHO Model List of Essential Medicines (49). However, regulatory approval and dosing protocols continue to be contingent upon the indication and setting.

In contrast, the evidence base for reproductive applications of pentoxifylline is more heterogeneous and less mature. The combination of pentoxifylline with vitamin E or other adjunctive therapies has the potential to enhance endometrial thickness, uterine perfusion, embryo quality, and inflammatory parameters, as indicated by the available studies (10, 55, 57–63). Nevertheless, there is a lack of high-quality evidence regarding live-birth outcomes, and surrogate outcomes have not been consistently correlated with increased pregnancy rates (61).

In general, these results suggest that off-label prescribing in gynecology should not be considered a standardized practice. The quality and consistency of the available evidence, the clinical relevance of reported outcomes, the degree of protocol standardization, the safety profile, and the patient-specific benefit–risk balance should all be considered when determining the level of clinical confidence. Consequently, methotrexate and letrozole can be distinguished as having comparatively mature evidence for specific indications, whereas filgrastim, sildenafil citrate, and pentoxifylline continue to require careful patient selection and additional confirmatory research. Misoprostol illustrates an alternative scenario in which regulatory variation across settings coexists with extensive evidence-based reproductive use.

Conclusion

Off-label prescribing remains an important component of women's reproductive healthcare, but the strength of evidence differs considerably across drugs and indications. Some applications are supported by relatively mature clinical evidence, whereas others remain dependent on careful patient selection and further confirmatory research. Rational off-label use should therefore be guided by evidence quality, indication-specific benefit–risk assessment, safety considerations, and appropriate clinical monitoring. Further high-quality studies are needed to standardize protocols, clarify long-term safety, and strengthen evidence-based clinical practice.

Declaration

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability
Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Not applicable.

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Supplementary Material
Supplementary Table 1 is provided in a single Microsoft Word document. The file can be downloaded from the following link.

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