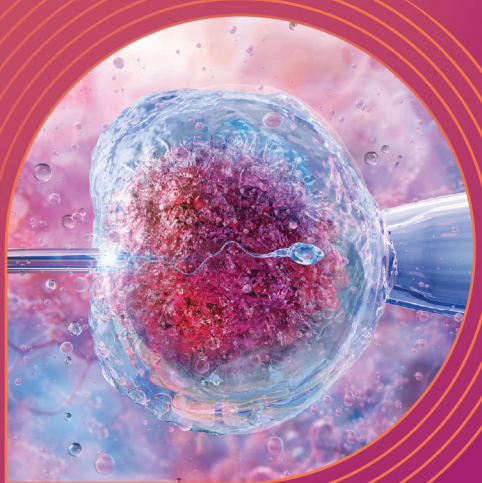
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Handbook of
Drugs in Infertility



Editors
Nandita Palshetkar
Rohan Palshetkar

Co-Editor
Ritu Khanna

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JAYPEE

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CHAPTER 1

Estrogens for Endometrial Preparation

KU Kunjimoideen

INTRODUCTION

Estrogens play a critical role in reproductive medicine, particularly in preparing the endometrium for embryo implantation during assisted reproductive techniques (ART) such as in vitro fertilization (IVF), frozen embryo transfer (FET), and donor oocyte cycles. Endometrial receptivity, where the uterine lining is appropriately prepared for embryo implantation, heavily depends on the proliferative actions of estrogen.[1] This chapter provides a comprehensive overview of the types of estrogens used, their mechanisms of action, protocols, clinical applications, and potential complications in the context of endometrial preparation.

ROLE OF ESTROGENS IN THE MENSTRUAL CYCLE

During the follicular (proliferative) phase of the menstrual cycle, estrogen stimulates the proliferation of endometrial cells, thickening the endometrial lining, which is crucial for supporting embryo implantation.[1] Estrogens:

- Stimulate endometrial proliferation
- *Upregulate estrogen and progesterone receptors* to sensitize the endometrium to hormonal signaling.
- *Enhance uterine blood flow* to support implantation.

In ART, exogenous estrogens are administered to mimic these physiological effects, ensuring the endometrium is sufficiently prepared for embryo transfer, especially in women with inadequate endogenous estrogen production (e.g., ovarian insufficiency and FET cycles).[2,3]

TYPES OF ESTROGENS USED FOR ENDOMETRIAL PREPARATION

Estrogens are critical in preparing the endometrium for embryo implantation, especially in patients undergoing ARTs such as IVF or FET. Various forms of exogenous estrogens are used to optimize endometrial receptivity, each with distinct pharmacokinetic profiles, efficacy, and clinical indications. Understanding the nuances of these estrogen types allows for tailored protocols that maximize patient outcomes while minimizing adverse effects.

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Oral Estrogens

Oral estrogens, including estradiol valerate and micronized estradiol, are among the most commonly prescribed forms for endometrial preparation. However, their efficacy is influenced by the first-pass metabolism through the liver, where a significant proportion of the hormone is metabolized before reaching systemic circulation. This necessitates higher doses to achieve therapeutic serum estradiol levels, typically ranging between 4 and 6 mg/day. The pharmacokinetics of oral estrogens can result in fluctuating serum levels, which may contribute to variability in endometrial response and patient outcomes.[4]

- *Dosing:* 4–6 mg/day, divided into two or three doses depending on the protocol and individual patient response.
- *Advantages:* Oral administration is straightforward and patient-friendly, often being the first-line option for many ART cycles.
- *Drawbacks:* Due to first-pass hepatic metabolism, oral estrogens can lead to inconsistent absorption and serum estradiol levels. This variability may require dose adjustments, and prolonged use can increase the risk of liver-related side effects, such as altered lipid metabolism and thromboembolism.

Recent research has focused on optimizing oral estrogen formulations to enhance bioavailability and reduce hepatic side effects, but they remain less favored for patients at high risk for thromboembolic events.

Transdermal Estrogens

Transdermal estrogens, delivered via patches, have gained popularity due to their ability to bypass first-pass metabolism, leading to more consistent and physiological serum estradiol levels. Estradiol patches, typically dosed at 50–100 mcg/day, provide a controlled release of hormone through the skin, ensuring steady-state concentrations that are well-suited for endometrial preparation.[5]

- *Advantages:* The avoidance of hepatic metabolism reduces the risk of systemic side effects, such as thromboembolism and liver enzyme elevation, compared to oral estrogens. Additionally, transdermal delivery ensures stable serum levels, reducing the need for frequent dosing adjustments.
- *Drawbacks:* Skin irritation is a common side effect, particularly with prolonged use, and patches need to be changed frequently (typically every 48–72 hours) to maintain optimal hormone levels. In addition, patients with compromised skin integrity or those who are sensitive to adhesives may find this method less tolerable.

The efficacy of transdermal estrogens in maintaining endometrial receptivity has been demonstrated in several studies, with comparable pregnancy rates to other forms of estrogen administration.

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Intramuscular Estrogens

Intramuscular (IM) injections of estradiol valerate or estradiol cypionate are a less frequently used but highly effective method for delivering estrogens. Doses range from 5 to 10 mg every 4 days, providing long-acting and stable estrogen levels, which can be advantageous in patients who require tight hormonal control.

- *Advantages:* IM estrogens ensure consistent and sustained hormone levels over several days, reducing the frequency of administration. This form is particularly useful in patients with gastrointestinal issues or those who experience fluctuating hormone levels with other routes of administration.
- *Drawbacks:* Injections can be painful, and dosing adjustments are less flexible than with oral or transdermal estrogens. The slow-release mechanism of IM estrogens can also lead to delayed peak concentrations, which may not be ideal for all patients.

Intramuscular estrogens are particularly useful in cases where other routes of administration have failed to achieve sufficient endometrial thickness (EMT), or in patients with a history of poor response to oral or transdermal forms.[6]

Vaginal Estrogens

Vaginal estrogen preparations are less commonly used in endometrial preparation protocols, but they offer a unique route that directly targets the reproductive tract, allowing for high local concentrations of estradiol with minimal systemic absorption. Vaginal tablets, creams, or rings can be utilized as an adjunct in combination with other forms of estrogen administration.

- *Advantages:* Vaginal estrogens provide localized effects, improving endometrial receptivity while minimizing systemic exposure. This is especially beneficial for patients who are at risk of systemic side effects from oral or transdermal estrogens, such as thromboembolic events or liver dysfunction.
- *Drawbacks:* Due to limited systemic absorption, vaginal estrogens may not provide sufficient hormone levels to achieve adequate endometrial preparation on their own. They are often used as a supplementary form of estrogen in conjunction with oral or transdermal methods.

Current studies suggest that vaginal estrogens may improve local endometrial conditions, particularly in women with thin endometria or those with resistance to other forms of estrogen therapy.[7] However, more research is needed to fully establish their role in ART protocols **(Table 1)**.

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TABLE 1: Types of estrogens used in endometrial preparation.

Type of estrogen	*Formulation*	*Route of administration*	*Advantages*	*Disadvantages*
Estradiol Valerate (E2V)	Oral, Intramuscular	Oral, IM	Widely available, flexible dosing	Variable bioavailability (oral), pain (IM)
Micronized estradiol	Oral	Oral	Easy administration	First-pass metabolism
Estradiol PATCHES	Transdermal	Transdermal	Steady hormone release, avoids liver metabolism	Skin irritation in some users
Vaginal estradiol	Vaginal tablets, creams, ring	Vaginal	Direct action on rep reductive tract	Limited systemic absorption

TABLE 2: Estrogen administration protocols for endometrial preparation.

Protocol	*Description*	*Indication*	*Duration*
Fixed protocol	Estrogen started on day 2–3 of the menstrual cycle	Most ART cycles, including FET	10–14 days
Flexible protocol	Estrogen administration with ultrasound monitoring	Poor responders, thin endometrium	Adjusted based on response
Sequential protocol	Combination of oral and transdermal estrogens for maximal effect	Women with history of thin endometrium	Varies (2–3 weeks)
Long protocol	Estrogen given for several weeks prior to ART cycle	Recurrent implantation failure, very thin endometrium	3–4 weeks

ESTROGEN PROTOCOLS FOR ENDOMETRIAL PREPARATION (TABLE 2)

The appropriate estrogen protocol for endometrial preparation is selected based on the patient's specific ART treatment cycle, such as FET, donor egg cycles, or IVF. Estrogen is crucial in developing a receptive endometrium, and the target thickness for successful implantation is generally considered to be ≥7 mm. Insufficient endometrial development is associated with lower implantation and pregnancy rates, necessitating the selection of an optimal protocol tailored to each patient's physiology. Below are the commonly utilized estrogen protocols, each with its own advantages based on clinical indications.[3]

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Fixed Protocol

The fixed protocol is one of the most straightforward approaches for endometrial preparation. Estrogen administration begins on day 2 or 3 of the menstrual cycle (or an artificial cycle if necessary) and continues for a period of 10–14 days. During this time, transvaginal ultrasound is used to monitor EMT. Once the endometrium reaches the target thickness, usually ≥7 mm, progesterone supplementation is initiated to transform the proliferative endometrium into the secretory phase, thus preparing it for embryo implantation.

- *Advantages:* This protocol offers simplicity and a predictable treatment schedule, making it an ideal option for patients with regular menstrual cycles or in controlled ovarian hyperstimulation cycles. It allows for clear scheduling of embryo transfer.
- *Considerations:* Patients who exhibit poor endometrial response to standard doses of estrogen may require adjustments in the estrogen dose or route of administration (e.g., transitioning from oral to transdermal estrogen). Moreover, in patients with polycystic ovary syndrome (PCOS) or those undergoing oocyte donation, response rates may vary, and individualized management may be needed.[6]

Flexible Protocol

The flexible protocol is more patient-tailored and provides flexibility in timing the start of progesterone based on the patient's individual response to estrogen. Estrogen is typically initiated early in the menstrual cycle, as in the fixed protocol, but the timing of progesterone addition is determined solely by the EMT rather than a predetermined number of days. Regular transvaginal ultrasound monitoring is performed, and only when the endometrium reaches the target thickness does progesterone supplementation begin.

- *Advantages:* This protocol allows for more individualized care, making it suitable for patients with variable endometrial responses to estrogen, such as those with a history of thin endometrium or prior implantation failures. It also reduces the risk of premature luteinization and mistiming the embryo transfer.
- *Considerations:* The flexible protocol requires more frequent monitoring (ultrasound and potentially hormonal) to ensure that progesterone is initiated at the optimal time, which may increase the patient's burden and healthcare costs.[6]

Sequential Protocol

The sequential protocol involves the combination of different forms of estrogen, such as oral and transdermal, to optimize endometrial preparation

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and achieve a higher likelihood of success. The rationale behind combining different routes of administration is to ensure both systemic and localized estrogen delivery, enhancing endometrial proliferation. Oral estrogens provide systemic levels of estrogen, while transdermal or vaginal estrogens offer more consistent and localized effects without the first-pass metabolism seen in oral formulations.

- *Advantages:* This approach is particularly beneficial in patients who have exhibited suboptimal endometrial response to a single form of estrogen, such as those with endometrial resistance or those experiencing hormonal fluctuations. By using multiple routes, the protocol enhances EMT while minimizing side effects such as gastrointestinal upset or fluctuating hormone levels.
- *Considerations:* Patients require careful monitoring to ensure that estrogen levels are within therapeutic ranges, and that the combination of routes is achieving the desired endometrial response. This protocol is more complex and requires precision in the timing and dosing of different estrogen forms.[5]

Long Protocol

The long protocol is specifically designed for patients with a history of thin endometrium, recurrent implantation failure, or those who have failed previous cycles despite adequate hormonal therapy. In this protocol, estrogen is administered over an extended period, sometimes lasting 3–4 weeks, to gradually stimulate the endometrial lining. This prolonged administration allows for more gradual and sustained endometrial proliferation, which may benefit patients who do not respond well to standard protocols.[6]

- *Advantages:* The long protocol can be particularly effective in poor responders, as the extended estrogen exposure allows for more time to build a receptive endometrium. Studies have shown that in patients with recurrent implantation failure or chronic thin endometrium, prolonged estrogen exposure may result in improved endometrial receptivity.
- *Considerations:* The extended nature of this protocol requires more frequent monitoring to avoid overthickening of the endometrium, which could paradoxically reduce implantation rates. Additionally, patients may experience prolonged side effects from estrogen, such as breast tenderness, bloating, or headaches, due to the extended hormonal exposure.

CLINICAL CONSIDERATIONS IN CHOOSING AN ESTROGEN PROTOCOL

The choice of estrogen protocol should be individualized based on the patient's medical history, response to prior ART cycles, and any underlying

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reproductive or endocrine conditions. In patients with a history of poor response to estrogen, alternative routes of administration (e.g., IM or transdermal estrogens) or a sequential protocol may enhance outcomes. Conversely, patients with a strong endometrial response may benefit from shorter or fixed protocols to minimize side effects and maximize efficiency. Hormonal levels (estradiol and progesterone) should be routinely monitored during these protocols to ensure optimal endometrial preparation.

Tailoring estrogen protocols to individual patient needs is essential for optimizing endometrial receptivity in ART cycles. Each protocol—fixed, flexible, sequential, or long—offers unique advantages based on patient-specific factors such as ovarian function, prior ART outcomes, and responsiveness to hormonal therapies. By carefully selecting and managing the estrogen protocol, clinicians can improve the likelihood of successful embryo implantation and pregnancy.[7]

CLINICAL OUTCOMES AND FINDINGS (TABLE 3)

The clinical effectiveness of estrogen therapy in ART cycles, particularly in preparing the endometrium for implantation, has been extensively validated through numerous studies. Achieving optimal EMT is critical for ensuring successful embryo implantation and pregnancy outcomes. Endometrial receptivity is directly influenced by estrogen levels, which promote endometrial proliferation, leading to a receptive environment for embryo transfer. Below, we summarize the key findings on the impact of EMT, pregnancy rates, and implantation failures.[8]

ENDOMETRIAL THICKNESS AND IMPLANTATION SUCCESS

Endometrial thickness plays a pivotal role in the success of ART cycles, including IVF and FET. Multiple studies have demonstrated that an

TABLE 3: Clinical outcomes associated with endometrial thickness in ART cycles.

Endometrial Thickness (mm)	*Implantation rate*	*Pregnancy rate*	*Clinical comment*
<6 mm	Low (5–10%)	Poor (10–15%)	Insufficient thickness, higher failure rates
7–8 mm	Moderate (20–30%)	Acceptable (30–40%)	Borderline thickness, may proceed with caution
9–12 mm	High (40–50%)	Optimal (50–60%)	Ideal range for implantation and pregnancy
>14 mm	Decreased	Lower success rates	May indicate overpreparation, lower success

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EMT of ≥7 mm is associated with significantly higher implantation rates. This threshold of 7 mm has been established as a marker of a receptive endometrium, below which implantation rates markedly decline.

A systematic review and meta-analysis by Liao Z et al. (2022) assessed the relationship between EMT and implantation success and found that pregnancy and live birth rates were highest when the EMT was within the range of 8–14 mm, with a significant drop-off in rates for EMT <7 mm.

PREGNANCY RATES AND ENDOMETRIAL THICKNESS

Pregnancy outcomes are closely linked to the thickness of the endometrium during ART cycles. A robust endometrial lining is essential for successful implantation, and several studies have highlighted the importance of achieving a sufficient EMT to optimize pregnancy rates.

A recent review by Hsueh YW et al. (2023) found that EMT is directly correlated with pregnancy outcomes in FET cycles.[8] The study examined over 5,000 FET cycles and reported that pregnancy rates were significantly higher in patients with EMT values ≥8 mm. The review also identified a linear relationship between increased EMT and higher cumulative pregnancy rates, suggesting that achieving an optimal EMT should be a primary focus in preparing patients for FET.

Further analysis of live birth rates shows that EMT is also a key determinant of neonatal outcomes, with thicker endometria associated with healthier pregnancy outcomes. Annemieke Kasius et al. (2014) noted that patients with EMT ≥9 mm had higher rates of successful live births, as well as reduced rates of miscarriage compared to those with thinner endometrium.[3]

IMPLANTATION FAILURES IN THIN ENDOMETRIUM

Thin endometrium (typically defined as EMT <7 mm) remains a significant challenge in ART, often resulting in implantation failure and recurrent pregnancy loss. Numerous studies have confirmed that patients with a thin endometrial lining experience significantly lower pregnancy rates, even when high-quality embryos are transferred. Thin endometrium may be attributed to several factors, including poor estrogen response, prior uterine surgeries, or intrauterine adhesions.

Implantation failures due to thin endometrium are commonly observed in patients with poor endometrial proliferation during FET or IVF cycles. These patients are less likely to achieve pregnancy due to inadequate receptivity of the endometrium, often requiring additional interventions to improve outcomes.

Recent advancements in hormone therapy have shown promising results in improving EMT for patients with a history of thin endometrium. Studies suggest that the use of transdermal or IM estrogen can significantly enhance endometrial growth in these patients. By bypassing the first-pass metabolism

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of oral estrogens, transdermal and IM routes allow for more stable and sustained estrogen delivery, which in turn supports better endometrial development.

Ogawa T et al. (2021) compared transdermal and IM estrogen therapy in patients with thin endometria and found that both routes were associated with increased EMT and higher pregnancy rates compared to oral estrogen therapy.

CLINICAL IMPLICATIONS

The clear relationship between EMT and reproductive outcomes highlights the critical importance of achieving optimal EMT during ART cycles. Clinicians should prioritize individualized protocols for estrogen therapy, ensuring close monitoring of endometrial growth through ultrasound measurements. For patients with thin endometrium, advanced therapeutic approaches, including sequential estrogen protocols or alternative routes of estrogen administration, may provide the necessary boost to enhance implantation success and improve overall pregnancy outcomes.[9]

COMPLICATIONS AND SIDE EFFECTS (TABLE 4)

While estrogen supplementation is critical for endometrial preparation, it is not without risks:

- *Thromboembolic events:* Oral estrogens are associated with increased risk of thromboembolic complications, particularly in patients with predisposing risk factors.[10]
- *Endometrial hyperplasia:* Long-term unopposed estrogen exposure may lead to endometrial hyperplasia or, in rare cases, malignancy.[11]
- *Side effects:* Common side effects include breast tenderness, nausea, and headache. Less frequent complications include gastrointestinal disturbances and mood changes.[12]

TABLE 4: Side effects and complications of estrogen therapy.

Complication	*Type of estrogen most affected*	*Incidence*	*Management strategies*
Thromboembolic events	Oral estrogens	Moderate	Switch to transdermal estrogens, lower dose
Nausea and gastrointestinal upset	Oral estrogens	Common	Administer with food or switch to transdermal
Endometrial hyperplasia	All forms if unopposed by progesterone	Low	Monitor closely, use with progesterone
Breast tenderness	All forms	Common	Symptomatic treatment or dose adjustment

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CONCLUSION

Estrogen is a cornerstone in endometrial preparation for ART cycles, particularly in women with inadequate endogenous estrogen production. When administered appropriately, estrogen significantly improves endometrial receptivity, implantation rates, and pregnancy outcomes. However, treatment protocols should be carefully tailored to each patient to maximize effectiveness and minimize risks.

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Nandita Palshetkar MD FCPS FICOG FRCOG (UK) is a Professor Emeritus, Department of Obstetrics and Gynecology, DY Patil School of Medicine, Navi Mumbai, Maharashtra, India. She is currently the FOGSI (Federation of Obstetric and Gynaecological Societies of India) Representative to International Federation of Gynecology and Obstetrics (FIGO) and also the Co-Chair of the Asia and Oceania Federation of Obstetrics and Gynaecology Reproductive Endocrinology and Infertility Committee. She has been the President of the Indian Society of Assisted Reproduction (2022–2024); Association of Maharashtra Obstetric and Gynaecological Societies (2020–2022); FOGSI (2019); Mumbai Obstetric & Gynecological Society (MOGS) (2016); Indian Association of Gynaecological Endoscopists (IAGE) (2017); and Maharashtra Chapter of ISAR (MSR) (2016–2018). She is the Founder and Medical Director of Bloom IVF and BAUFICI Genetics, heading 11 in vitro fertilization (IVF) centers all over India. She has delivered over 100 orations and given over 1,000 talks at national and international conferences. She has written over 100 textbook chapters, edited several books, and published papers in national and international journals. She has received 18 national and international awards including the Bharat Gaurav Award at the House of Commons in the UK. She is an Infertility Specialist, Lilavati Hospital IVF Center, Mumbai. Most recently, she has been conferred the Fellowship of the Royal College of Obstetricians and Gynaecologists for her work.

Rohan Palshetkar MS (Obs and Gyne) FRM BDRME ADRME is an ART Consultant and Endoscopic Surgeon. He is a Professor, Department of Reproductive Medicine, DY Patil Medical College, Mumbai, Maharashtra, India, and is also the Unit Head of DY Patil Bloom IVF and Opera House Bloom IVF, Mumbai. He is currently the Chairperson of the FOGSI Young Talent Promotion Committee; First Joint Secretary, All Maharashtra Association of Obstetrical and Gynaecological Societies, Joint Treasurer of Maharashtra Chapter of IAGE and the Managing Committee Member of Indian Society of Assisted Reproduction, Maharashtra Chapter of ISAR and Mumbai Obstetric and Gynecological Society (MOGS). He has delivered the YUVA-ISAR Oration, MSR Yuva Oration and the FOGSI Kamini Rao Yuva Oration. Besides this, he has delivered several talks and contributed several publications for FOGSI and MOGS. He has multiple publications and delivered over 150 talks. He is the Recipient of the Asia & Oceania Federation of Obstetrics and Gynaecology Young Gynecologist Award. He has won the prestigious FOGSI Corion, Shanti Yadav Award, Kumud Tamaskar and Praveen Mehta Awards for his research papers. He has also won the best Youth Council Member Award for MOGS twice. Besides his academic awards, he has received the Times Network India Healthcare Award and has also received the We for Stree Puraskar at the hands of the Governor of Maharashtra, Honorable Bhagat Singh Koshyari.

Ritu Khanna MS (Obs and Gyne) FICOG is an ART Consultant and Endoscopy Surgeon. She is the Director and ART Consultant, Department of Obstetrics and Gynecology, Khanna Medical Centre (Fertility Clinic), Varanasi, Uttar Pradesh, India. She is Currently the Vice President Indian Fertility Society, Secretary of Society of Fetal Medicine UP Chapter. She was the Chairperson of FOGSI Food & Drug and Medico Surgical Equipment Committee (2021–2024). She is Editor of ten FOGSI Books, Co-Editor one Book and Authored ten Chapters in Other Publications. She has delivered more than 600 talks and has various prestigious awards to her credit including Dr BC Roy award. She has passion to work for women's health.

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