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Evaluating the effectiveness and adverse effects of oral versus transdermal estradiol for endometrial preparation in frozen-thawed embryo transfer: a randomized controlled trial

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Abstract

Background Endometrial preparation significantly influences the success of embryo transfer procedures. Although both oral and transdermal estradiol are common methods for endometrial priming, their efficacy and potential side effects remain uncertain. This randomized controlled trial aims to compare the effectiveness of oral and transdermal estradiol in endometrial preparation, while also evaluating their respective side effects in patients undergoing assisted reproduction treatments.

Method This randomized clinical trial (ISRCTN15301227) was conducted at Hung Vuong Hospital between July 2020 and March 2022. Among 550 eligible patients undergoing frozen embryo transfer cycles, we included 380 patients for the study. The study protocol and all materials received approval from the Ethics Committee of Hung Vuong Hospital (1315/CN-HĐĐĐ). Participants were randomly assigned to one of two groups: Group A (n =190) received oral estradiol at an initial dose of 4 mg per day for 7 days, with the dose increased according to clinical response. Group B (n =190) received transdermal estradiol at an initial dose of 2 measures of 2.5 g estradiol gel per day for 7 days, with the dose similarly increased according to clinical response. Treatment in both groups began on days 2–3 of the menstrual cycle, with the maximum duration of estradiol administration being 27 days. We compared estradiol levels on the day of progesterone administration, duration of treatment, total estradiol dose, endometrial thickness, pregnancy outcomes, and any observed side effects between the two groups.

Results Group A exhibited significantly higher estradiol levels on the day of progesterone administration compared to Group B (270.5 pg/ml versus 186.5 pg/ml, $p<0.001$). However, the comparison revealed no significant difference in endometrial thickness between the two groups (10.5 mm versus 10.6 mm, $p=0.85$). Furthermore, pregnancy rates including positive human chorionic gonadotropin, clinical pregnancy, ongoing pregnancy, live birth, and pregnancy failure were also found to be similar between the two groups. Notably, a greater proportion of patients in Group A experienced mild side effects compared to those in Group B (20.3% versus 10.1%, respectively; n =37 versus n =18), and this discrepancy was found to be statistically significant ($p=0.007$).

Conclusion Transdermal estradiol offers comparable endometrial thickness and pregnancy outcomes, along with improved patient compliance and fewer side effects compared to oral estradiol.

Keywords IVF, Frozen-thawed embryo transfer, Transdermal estradiol, Pregnancy outcome

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Background

Nowadays, in vitro fertilization (IVF) has become an effective intervention for assisting infertile couples in achieving pregnancy [1]. Typically, embryos are created using intracytoplasmic injection (ICSI) and cultured in an artificial system before being cryopreserved for transfer in a subsequent cycle. This freeze-all strategy has gained widespread popularity worldwide [2]. The preparation of the endometrium for embryo transfer is a crucial step in this process. The choice of protocol depends on various factors, including the patient's medical history, hormonal status, and the preferences of the treating physician [3]. Among these protocols, hormone replacement therapy has emerged as a popular method for preparing the endometrium [4]. In brief, estrogen priming stimulates the growth of endometrium through oral or transdermal administration. Regular monitoring via transvaginal ultrasound and blood tests are carried out to assess endometrial thickness and estrogen levels. Once the desired parameters are achieved, progesterone supplementation is introduced to mimic the luteal phase. Progesterone support continues after embryo transfer, and may extend into early pregnancy to enhance implantation and support the luteal phase [5].

The choice between the oral and transdermal route is based on several factors [6]. Oral estradiol, delivered via tablets or capsules, is a simple and well-tolerated method [7]. Upon ingestion, oral estradiol is absorbed through the gastrointestinal tract and enters the bloodstream, where it is distributed to target tissues [8]. Subsequently, estradiol undergoes metabolism in the liver [9]. In the context of endometrial preparation for frozen embryo transfer (FET), oral estradiol stimulates endometrial growth, creating a receptive environment for embryo implantation. However, due to its direct effects on circulation, oral estradiol can be associated with gastrointestinal side effects [10].

Conversely, the transdermal estradiol administration is an alternative method for endometrial preparation in FET. It involves the application of estradiol patches, gels, or creams directly to specific areas of the skin, such as the abdomen, thighs, or upper arms. Unlike oral estradiol, transdermal estradiol bypasses hepatic metabolism, resulting in more consistent hormone levels and potentially fewer side effects [11]. This route also offers a lower risk of gastrointestinal side effects. However, it may be associated with skin irritation or adhesive reactions at the application site [12].

In this randomized controlled trial (RCT), we aimed to evaluate the effectiveness and adverse effects of oral versus transdermal estradiol for endometrial preparation in FET cycles. By comparing these two administration methods, we sought to provide valuable insights into optimizing FET success rates and improving patient compliance in assisted reproduction.

Materials and methods

Study design and population

This randomized clinical trial (ISRCTN15301227) was conducted at Hung Vuong Hospital (1315/CN-HĐĐĐ) between July 2020 and March 2022. The study included patients aged 18–45 who underwent IVF followed by FET cycles and had no history of uterine intervention or underlying medical conditions, demonstrating a willingness to adhere to the research protocol. Patients with a body mass index (BMI) greater than 30, congenital uterine malformations, acquired lesions such as fibroids, adenomyosis, endometriosis, systemic diseases, those undergoing donor cycles or surrogacy, and cycles involving preimplantation genetic testing were excluded from the study.

A computer-generated random number list was created using "2 4 6" block randomization. Envelopes were prepared in advance by an individual who is not involved in the trial and had no knowledge of the participants' characteristics. These envelopes were then sealed. Participants were randomly assigned to one of two groups by selecting an envelope. Specifically, Group A (n =190) received oral estradiol, while Group B (n =190) received transdermal estradiol. The use of these envelopes helped maintain blinding and prevent bias. Researchers responsible for administering treatments, collecting data, and assessing outcomes were also blinded to the treatment allocation. Additionally, data analysis was performed by a statistician who was blinded to the group assignments.

We collected information regarding patients demographic and clinical characteristics. Relevant data included patient age, BMI (body mass index), AMH (antimüllerian hormone), infertility duration, subfertility, and indication for treatment. Regarding primary outcomes, we compared estradiol levels on the day of progesterone administration, duration of treatment, total estradiol dose, and endometrial thickness on the day of progesterone injection. Estradiol levels on the day of progesterone administration were measured in pg/mL to assess the efficacy of endometrial preparation. Duration of treatment was defined as the total number of days patients received estradiol. Total estradiol dose was measured in milligrams to evaluate the cumulative hormone exposure. Endometrial thickness on the day of progesterone injection was measured in millimeters via ultrasound to determine the adequacy of the endometrial lining for embryo transfer.

Regarding the secondary outcomes, we compared pregnancy outcomes and any observed side effects between the two groups. In this study, we confirmed the

human chorionic gonadotropin (hCG) results through the presence of positive hCG levels. Clinical pregnancy was defined by the presence of a viable fetal heart rate, as determined between 7 and 8 weeks' gestation. Ongoing pregnancy was categorized as pregnancies that persisted beyond 20 weeks' gestation. Live births referred to the total number of successfully delivered babies. Pregnancy failure was the pregnancy loss at any stage. Observed side effects included any adverse events or symptoms reported by patients during the study period. To gather comprehensive data on side effects, we conducted in-depth interviews with participants to collect their experiences with the drug administration methods. Additionally, we thoroughly reviewed the drug instructions with each patient at the start of the study, ensuring they were well-informed about correct usage and encouraging them to report any confusion or difficulties.

Sample size calculation

The sample size was determined through a power analysis to ensure adequate statistical power. Using other outcomes for calculation would have required a large or unequal sample size due to comparable rates between the groups in previous studies. Therefore, to make the study feasible, we based our calculations on a published study that reported a cycle cancellation rate of 6.45% for the oral estradiol group and 0.83% for the transdermal estradiol group [13]. Although cancellation rate was not the primary outcome of our study, and indeed, no patients in our study experienced cycle cancellation, this approach allowed us to estimate a manageable sample size. With a significance level (α) of 0.05 and a power (1-β) of 80%, we initially calculated that a total of 340 participants were needed. To account for an anticipated 10% loss to follow-up, we increased the sample size to 380 participants (190 per group).

Endometrial preparation using oral estradiol

On days 2–3 of the menstrual cycle, patients began taking 2 mg of oral estradiol (Progynova, Bayer, Germany) twice daily. The dosage was increased every 5 days in 4 mg intervals, up to a maximum of 16 mg daily. For the next 14–16 days, transvaginal sonography was used to assess the endometrium thickness. To ensure consistency in measuring endometrial thickness, the same ultrasound machine was used throughout the study, and the ultrasound was performed by an experienced physician following an established protocol at our department. Luteal support was initiated once the endometrial thickness reached 8—14 mm with a triple-line pattern. Patients received detailed instructions on medication usage. In the event of missing medication for more than 2 consecutive days, patients must inform the research team. To control medication dosage, patients were required to retain both the prescription and the medication box. Additionally, researchers contacted patients via phone weekly to remind the medication intake.

Endometrial preparation using transdermal estradiol

On days 2–3 of the menstrual cycle, patients began using 2.5 g of transdermal estradiol (Oestradiol Besins, Besins Manufacturing, Belgium) twice a day. The dosage was increased up to a maximum of 20 g daily. For the next 14–16 days, transvaginal sonography was used to assess the endometrium thickness. To ensure consistency in measuring endometrial thickness, the same ultrasound machine was used throughout the study, and the ultrasound was performed by an experienced physician following an established protocol at our department. Luteal support was initiated once the endometrial thickness reached 8—14 mm with a triple-line pattern. Patients were instructed to apply transdermal estradiol and allow 2–5 min to dry. They were advised not to wash the area where the medication was applied for at least 1 h. In the event of a missed dose of estrogen gel, patients were instructed to apply it normally if it was within 12 h of the usual time; otherwise, they were advised to skip the missed dose, wait, and apply the next estrogen dose. To control medication dosage, patients were required to retain both the prescription and the medication box. Additionally, researchers contacted patients via phone weekly to remind the medication intake.

Ethical consideration

The study protocol and all materials received approval from the Ethics Committee of Hung Vuong Hospital (1315/CN-HĐĐĐ). The written informed consent was obtained from all participants. We also registered the trial (ISRCTN15301227).

Statistical analyses

Descriptive statistics were used to summarize patient characteristics. Continuous variables were presented as means with standard deviations, and categorical variables as frequencies and percentages. For quantitative data with a normal distribution, we used independent sample t-test and data were reported as a mean standard deviation. For qualitative data, we used Chi-square and Fisher-exact test. A p-value less than 0.05 was considered statistically significant. We used R software to analyze data.

Results

Figure 1 illustrates the CONSORT flow diagram. A total of 550 participants were recruited to the study. Among them, we excluded 160 patients due to not meeting the inclusion criteria, and 10 patients who refused to participate. The remaining 380 patients were then randomly assigned to Group A (receiving oral estradiol) with 190 patients and Group B (receiving transdermal estradiol) with 190 patients. Regarding Group A, 8 patients were further excluded from the analysis due to bleeding during the endometrial preparation. Regarding Group B, 12 patients were excluded. Among them, 3 were bleeding during the endometrial preparation, 8 were diagnosed with thin endometrium, and 1 was due to the uterine polyp. Patients were included in the study between July 2020 and July 2021. Follow-up was completed on March 2022.

Table 1 presents the patient characteristics of two groups. Both groups exhibited similar demographic profiles, with no significant differences observed in age (32.3 ± 4.5 vs. 31.7 ± 4.1, $p=0.141$), BMI (22.2 ± 3.2 vs. 22.1 ± 3.1, $p=0.794$), AMH (4.5 ± 3.8 vs. 4.8 ± 3.3, $p=0.348$), and infertility duration (4.5 ± 2.8 vs. 4.4 ± 2.9, 0.965). Additionally, the distribution of subfertility, including primary and secondary fertility, was comparable between the two groups. The most common indications for treatment, such as anovulation, cervical and tubal factors, were consistent between Group A and Group B, with no notable discrepancies in their distribution. These findings suggest that the patient cohorts in both groups were well-matched in terms of baseline characteristics.

Table 2 compares various characteristics of frozen embryo transfer cycle between Group A and Group B. It reveals that the duration of treatment and total estradiol dose were similar between the groups, with no significant differences observed (p-values of 0.821 and 0.670, respectively). However, there was a notable discrepancy in peak estradiol levels on the day of progesterone injection, with Group A showing a significantly higher peak compared to Group B (270.5 pg/ml vs. 186.5 pg/ml, $p<0.001$). Endometrial thickness on the day of progesterone injection did not differ significantly between the groups ($p=0.850$). Additionally, the distribution of embryo transfers between Day 3 and Day 5 showed no significant variation ($p=0.170$). Similarly, the number and quality of embryos transferred did not significantly differ between the groups. Overall, while peak estradiol levels differed between the two groups, other parameters such as treatment duration, total estradiol dose, and endometrial thickness did not exhibit significant differences, suggesting that the method of estradiol administration may

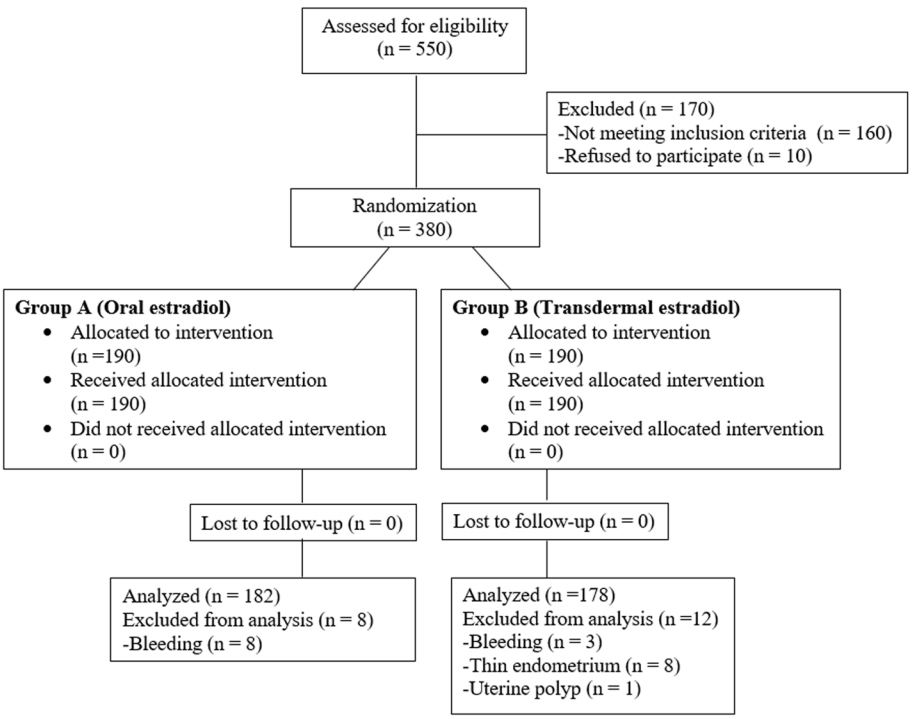

Fig. 1 CONSORT flow diagram of the study. CONSORT flow diagram illustrating the progress of participants through each stage of the randomized controlled trial comparing the effectiveness and adverse effects of oral and transdermal estradiol. The diagram includes the number of participants assessed for eligibility, randomized, allocated to each intervention, received each intervention, and analyzed for the primary outcome. Reasons for exclusion, dropout, and loss to follow-up are also detailed at each stage

Table 1 Baseline characteristics of the control and experimental groups

Patient characteristics	Group A (*n* = 182)	Group B (*n* = 178)	*p*-value
Age, years (mean ± SD)	32.3 ± 4.5	31.7 ± 4.1	0.141
BMI, kg/m^2 (mean ± SD)	22.2 ± 3.2	22.1 ± 3.1	0.794
AMH, ng/mL (mean ± SD)	4.5 ± 3.8	4.8 ± 3.3	0.348
Infertility duration, years (mean ± SD)	4.5 ± 2.8	4.4 ± 2.9	0.965
Subfertility, n (%)			
1/ Primary	106 (58.2)	109 (61.2)	0.563
2/ Secondary	76 (41.8)	69 (38.8)	
Indication for treatment, n (%)			
1/ Anovulation	37 (20.3)	36 (20.2)	0.362
2/ Tubal factor	48 (26.4)	47 (26.4)	
3/ Uterine factor	0 (0)	1 (0.6)	
4/ Cervical factor	46 (25.3)	56 (31.5)	
5/ Male factor	0 (0)	1 (0.6)	
6/ Other	15 (8.2)	15 (8.4)	
7/ Unexplained	36 (19.8)	22 (12.4)	

Group A: Oral estradiol, Group B: Transdermal estradiol

BMI Body mass index, *AMH* Anti-müllerian hormone, *SD* standard deviation

A *p*-value of < 0.05 was considered significant

Table 2 Baseline characteristics of the frozen embryo transfer cycles

Characteristics	Group A (*n* = 182)	Group B (*n* = 178)	*p*-value
Duration of treatment, days (mean ± SD)	19.4 ± 2.2	19.5 ± 2.4	0.821
Total estradiol dose, mg (mean ± SD)	63.0 ± 20.5	64.0 ± 21.2	0.670
Peak estradiol on day of progesterone injection, pg/mL	270.5 (197.0 – 394.0)	186.5 (126.0 – 258.0)	< 0.001
Endometrial thickness on day of progesterone injection, mm (mean ± SD)	10.5 ± 1.1	10.6 ± 1.3	0.850
Age of transferred embryos, n (%)			
1/ Day 3 embyro	21 (11.5)	13 (7.3)	0.170
2/ Day 5 embryo	161 (88.5)	165 (92.7)	
No. of embryo transferred, n (%)			
1/ 1	157 (86.3)	153 (86.0)	0.999
2/ ≥ 2	25 (13.7)	25 (14.0)	
No. of good-quality embryo transferred, n (%)			
1/ 0	41 (22.5)	51 (28.7)	0.418
2/ 1	139 (76.4)	126 (70.8)	
3/ 2	2 (1.1)	1 (0.6)	

Group A: Oral estradiol, Group B: Transdermal estradiol

SD standard deviation

A *p*-value of < 0.05 was considered significant

influence peak estradiol levels but not other measured parameters.

Table 3 presents the outcomes of oral estradiol compared to transdermal estradiol in terms of positive hCG, clinical pregnancy, ongoing pregnancy, live birth, and pregnancy failure rates. There was a slight difference in positive hCG, with 99 (54.4%) positive hCG results in Group A and 105 (59.0%) in Group B, but this difference was not statistically significant ($p = 0.379$). Similarly, the rates of clinical pregnancy were comparable between the two groups, with 95 (52.2%) in Group A and 100 (56.2%) in Group B ($p = 0.474$). The rates of ongoing pregnancy

Table 3 Pregnancy outcomes of patients between the control and experimental groups

Characteristics	Group A (*n* = 182)	Group B (*n* = 178)	*p*-value
Positive hCG, n (%)	99 (54.4)	105 (59.0)	0.379
Clinical pregnancy, n (%)	95 (52.2)	100 (56.2)	0.474
Ongoing pregnancy, n (%)	64 (35.2)	68 (38.2)	0.550
Live birth, n (%)	60 (33.0)	61 (34.3)	0.794
Pregnancy failure, n (%)	18 (9.8)	15 (8.4)	0.417

Group A: Oral estradiol, Group B: Transdermal estradiol

hCG human chorionic gonadotropin

A *p*-value of < 0.05 was considered significant

Table 4 Side effects of patients between the control and experimental groups

Characteristics	Group A (*n* = 182)	Group B (*n* = 178)	*p*-value
Side effect, n (%)			
1/ Yes	37 (20.3)	18 (10.1)	0.007
2/ No	145 (79.7)	160 (89.9)	
Side effect, n (%)			
1/ Convenience	145 (79.7)	160 (89.9)	< 0.001
2/ Headache	10 (5.5)	1 (0.6)	
3/ Vomiting	5 (2.7)	1 (0.6)	
4/ Epigastric pain	18 (9.9)	4 (2.2)	
5/ Dermatitis	0 (0)	12 (6.7)	
6/ Hot flush	4 (2.2)	0 (0)	

Group A: Oral estradiol, Group B: Transdermal estradiol

A *p*-value of < 0.05 was considered significant

were 64 (35.2%) in Group A and 68 (38.2%) in Group B, demonstrating no significant difference ($p = 0.550$). Additionally, the rates of live birth were similar, with 60 (33.0%) in Group A and 61 (34.3%) in Group B ($p = 0.794$). Both groups had relatively low rates of pregnancy failure, with 18 (9.8%) in Group A and 15 (8.4%) in Group B, showing no significant difference ($p = 0.417$). Overall, these findings suggest that both oral and transdermal estradiol may be equally effective in supporting successful pregnancy outcomes in patients undergoing assisted reproductive technology treatments.

Table 4 shows the side effects of patients between the control and experimental groups. Interestingly, Group A reported a significantly higher incidence of side effects compared to Group B (20.3% vs. 10.1%, $p = 0.007$). Group A also experienced a higher frequency of epigastric pain (9.9% vs. 2.2%, $p < 0.001$). However, Group B had a slightly higher incidence of dermatitis (6.7% vs. 0%, $p < 0.001$). Other side effects such as headache, vomiting, and hot flushes were infrequent in both groups. These findings suggest that transdermal estradiol may be associated with fewer side effects and greater convenience compared to oral estradiol administration.

Discussion

This RCT study evaluated the effectiveness and side effects of oral versus transdermal estradiol for endometrial preparation in patients undergoing FET. To our knowledge, our study represents the largest population cohort in this context. Our findings suggest that transdermal estradiol offers comparable endometrial thickness and pregnancy outcomes along with improved patient compliance and fewer side effects compared to oral estradiol.

Regarding pregnancy outcomes, our study did not identify any differences in positive hCG results, clinical pregnancy, ongoing pregnancy, pregnancy failure, or live birth rates between the two groups. These findings are consistent with the majority of published RCT studies [3, 7, 14, 15]. One RCT notably suggested that transdermal estradiol could result in higher rates of ongoing pregnancy and live birth compared to the oral route [16]. However, this study was constrained by its small sample size.

Our study observed that while the oral estradiol group demonstrated significantly higher peak serum estradiol levels on the day of progesterone administration compared to the transdermal group (270.5 pg/ml vs. 186.5 pg/ml, $p < 0.001$), these elevated levels did not translate to improved endometrial thickness. Both groups achieved similar endometrial thickness on the day of progesterone injection indicating that despite the pharmacokinetic differences, the endometrial response appear to be equivalent between the two administration routes. This finding aligns with previous RCT studies [7, 14]. However, some studies suggest that the transdermal route may lead to better endometrial thickness after 10 days of treatment [3, 15].

The physiological differences between oral and transdermal estradiol are significant. Oral estradiol undergoes first-pass metabolism in the liver, leading to higher peak serum estradiol levels and potential fluctuations in hormone levels [17]. This can result in more systemic side effects, such as gastrointestinal discomfort and alterations in liver enzyme levels. In contrast, transdermal estradiol can produce a sustained release, bypassing hepatic first-pass metabolism, resulting in more stable serum estradiol levels and a reduced risk of liver-related side effects [18]. This stable hormone delivery may

contribute to the lower incidence of side effects observed in the transdermal group.

An important aspect of our findings was the significant difference in the side effect profiles between the two methods. Oral estradiol was associated with more frequent mild side effects such as gastrointestinal discomfort, likely due to first-pass metabolism in the liver which is bypassed by the transdermal route. The transdermal group, in contrast, exhibited lower overall side effects. This could play a crucial role in patient compliance and preference, particularly in long-term treatments or in populations sensitive to gastrointestinal side effects. The clinical implications of our study are significant for healthcare providers who manage endometrial preparation for FET. While efficacy remains comparable between administration routes, differing side effect profiles suggest that patient-specific factors should guide the choice of estradiol administration route. Considerations such as previous hormone tolerance, comorbid conditions like liver function abnormalities or cardiovascular risk factors, and personal preference should inform this decision-making process.

Our study adds to the existing knowledge by providing robust evidence from a large cohort that supports the use of transdermal estradiol as a viable alternative to oral estradiol for endometrial preparation. It highlights the importance of considering side effect profiles and patient compliance when selecting an estradiol administration route. Moreover, our findings underscore the need for personalized treatment approaches in reproductive medicine.

However, our study has limitations, being conducted at a single center, which may limit the generalizability of findings to broader populations. Future multicenter studies are needed to validate our results across diverse demographic and ethnic groups. Additionally, studies could investigate the pharmacogenomic aspects of estradiol metabolism which may explain the variability in side effects and efficacy between individuals.

Conclusions

Transdermal estradiol offers comparable endometrial thickness and pregnancy outcomes, along with improved patient compliance and fewer side effects compared to oral estradiol.

Abbreviations

IVF	In vitro fertilization
ICSI	Intracytoplasmic injection
FET	Frozen embryo transfer
RCT	Randomized controlled trial
BMI	Body mass index
AMH	Anti-müllerian hormone
hCG	Human chorionic gonadotropin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43043-024-00204-7.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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None.

Authors' contributions
Thuy Thi-Thanh Tran and Tuyet Thi-Diem Hoang conceptualized the study. Thuy Thi-Thanh Tran, Trang Nguyen-Khanh Huynh and Loc Thai Ly collected data and performed statistical analysis. Huy Phuong Tran and Son Truong Dang investigated the results. Huy Phuong Tran, Tuyet Thi-Diem Hoang and Trang Nguyen-Khanh Huynh interpreted the data and drafted the manuscript. All authors approved the final version of the study.

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Availability of data and materials
We attached a Supplementary file to our submission. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol and all materials received approval from the Ethics Committee of Hung Vuong Hospital (1315/CN-HĐĐĐ). Approved 11 June 2020. Data were handled with strict confidentiality, ensuring the privacy of the participants, following the patient consent. We also registered the trial: ISRCTN, ISRCTN15301227. Registered 2 July 2020, https://www.isrctn.com/ISRCTN15301227.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no conflicts of interest.

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